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NOVEL ALANYL-AMINOPEPTIDASE INHIBITORS FOR FUNCTIONALLY INFLUENCING DIFFERENT CELLS AND TREATING IMMUNOLOGICAL, INFLAMMATORY, NEURONAL, AND OTHER DISEASES

Aminopeptidase N (APN, CD13, EC 3.4.11.2) belongs to the (ubiquitously present) group of alanyl aminopeptidases predominantly occurring as a membrane protein of type II, as does the cytosolic soluble alanyl aminopeptidase (EC 3.4.11.14; Puromycine-sensitive aminopeptidase, aminopeptidase PS, ence-phaline-degrading aminopeptidase). Both peptidases act metal-dependant and catalyse the hydrolysis of peptide bonds after N-terminal amino acids of oligopeptides, in the case of APN with preference for alanine at the N-terminal end (A. J. Barrett et al.: Handbook of Proteolytic Enzymes, Academic Press, 1998). All inhibitors of aminopeptidase N also inhibit the cytosolic alanyl amino-peptidase, while specific inhibitors exist for the cytosolic aminopeptidase (M. Komodo et al.; Bioorg. and Med. Chem. 9, 121(2001).

For both enzymes, important biological functions were demonstrated in different cell systems. This is true for the immune system (U. Lendeckel et al.: Intern. J. Mol. Med. 4, 17, 1999; T. Osada et al.: J. Neurosciences 19, 6068 (1999); published International Patent Application WO 01/89569 A1; published International Patent Application No. WO 02/053170 A3; International Patent Application No. PCT/EP 03/07199), the neuronal system (published International Patent Application No. WO 02/053169 A2 and German Patent Application No. 103 37 074.9), the fibroblasts (German Patent Application No. 103 30 842.3), the keratinozytes (published International Patent Application No. WO 02/053170 A3), die sebaceous gland cells/Sebocytes (International Patent Application No. PCT/EP 03/02356), for tumors and for virus infections. The receptor for corona viruses is suppressed by inhibitors of this peptidase (D. P. Kontoyiannis et al.: Lancet 361, 1558, 2003).

For both alanyl aminopeptidases, distinguishable inhibitors are known (M.-C. Fournie-Zaluski and B. P. Roques, in: J. Langner and S. Ansorge, Ectopeptidases, Kluwer Academic/Plenum Publishers, p 51 (2002); M. Komodo et al.: Bioorg. and Med. Chem. 9, 121, 2001; Y. Hashimoto: Bioorg. and Med. Chem. 10, 461, 2002).

The isolated inhibition of the alanyl aminopeptidases and of analogous peptidases, but particularly the combined inhibition of these peptidases and of dipeptidyl peptidase IV and of analogous enzymes results into a strong inhibition of the DNA synthesis and, thereby, of the cell proliferation in immune cells as well as into a change of the cytokine production, particularly into an induction of the immunoregulatory effective TGF-β1 (published International Patent Application No. WO 01/89569 A1; published International Patent Application No. WO 02/053170 A3). For regulatory T-cells, alanyl aminopeptidase inhibitors effect a strong induction of TGF-β1 (International Patent Application No. PCT/EP 03/07199). In the neuronal system, a reduction or deceleration, respectively, of acute and chronic cerebral deterioration processes by an inhibition of alanyl aminopeptidases, but particularly by a combined inhibition of the alanyl amino-peptidases and of dipeptidyl peptidase IV or of analogous enzymes was demonstrated (published International Patent Application WO 02/053169 A3 and German laid-open Patent Application No. 103 37 074.9). It could be shown, too, for fibroblasts (German laid-open Patent Application No. 103 30 842.3), keratinocytes (published International Patent Application No. WO 02/053 170 A3) and Sebatocytes (International Patent Application No. PCT/EP 03/02356) that an inhibition of alanyl aminopeptidases, but particularly a combined inhibition of the two peptidase systems effects an inhibition of the growth and a change of the cytokine production.

Thus, there results the surprising fact that the alanyl aminopeptidases as well as analogously working enzymes perform fundamental central biological functions in several organs and cell systems, and that an inhibition of these peptidases alone, but particularly a combined inhibition of these enzymes together with an inhibition

of the dipeptidyl peptidase IV and of analogous peptidases, represents a novel effective therapeutic principle for the treatment of different diseases which are chronic in most of the cases.

By using accepted animal models, the Inventors could demonstrate that, particularly, the combined administration of inhibitors of both peptidases effects, in fact, also *in vivo* an inhibition of the growth of different cell systems and a suppression of an excessive immune response, of chronic-inflammatory events as well as of cerebral damage (published International Patent Application WO 01/89569 A1).

The results achieved up to now were, predominantly, obtained by using known inhibitors of alanyl aminopeptidases, which are described in the literature and are, in part, commercially available, alone and, particularly, in combination.

It was an object of the present invention to find further effective inhibitors of alanyl aminopeptidases. In particular, lower molecular weight compounds and easily accessible compounds were to be found which allow an effective inhibition of alanyl aminopeptidases and of analogous enzymes.

Surprisingly, in the course of a high-throughput screening of substance data bases, there were now found novel, predominantly non-peptidic low-molecular inhibitors for the alanyl aminopeptidases.

The invention relates to novel substances specifically inhibiting peptidases cleaving Ala-p-nitroanilide.

Specifically, the present invention relates to substances of the general formulae A1 to A14 according to claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 and 27 as well as tautomers and stereoisomers of said compounds of the general formulae

A1 to A14, as well as pharmaceutically acceptable salts, salt derivatives, tautomers and stereoisomers thereof, for a use in the medical field.

In a specific embodiment, the present invention relates to specific compounds having the specific formulae A1.001 to D14.003 which are covered by the above general formulae A1 to A14, which compounds, as examples and without restricting them to those, are listed in claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and 28 in the form of tables, as well as tautomers and stereoisomers of said compounds of the general formulae A1.001 to A14.007, and pharmaceutically acceptable salts, salt derivatives, tautomers and stereoisomers thereof, for a use in the medical field.

Moreover, the invention relates to pharmaceutical compositions comprising at least one compound having one of the general formulae A1 to A14, optionally in combination with per se known and usual carriers and adjuvants.

Moreover, the invention relates to cosmetic compositions comprising at least one compound having one of the general formulae A1 to A14, optionally in combination with per se known and usual carriers and adjuvants.

Furthermore, the invention relates to the use of at least one compound of one of the general formulae A1 to A14 or of at least one of the above-mentioned pharmaceutical or cosmetic compositions for inhibiting the activity of alanyl aminopeptidases or of analogous enzymes, in a manner alone or in combination with inhibitors of dipeptidyl peptidase IV (DP IV) or of analogous enzymes.

Furthermore, the invention relates to the use of at least one compound of one of the general formulae A1 to A14 or of at least one of the above-mentioned pharmaceutical or cosmetic compositions for topically influencing the activity of alanyl

aminopeptidases or of analogous enzymes, in a manner alone or in combination with inhibitors of DP IV or of analogous enzymes.

Moreover, the invention relates to the use of at least one compound of one of the general formulae A1 to A14 or of at least one of the above-mentioned pharmaceutical or optionally also cosmetic compositions for a prophylaxis and therapy of a number of diseases which, as a matter of an exemplary description, are claimed in claims 33 to 45. In particular embodiments, without that this should be interpreted as restricting the invention, compounds of the general formulae A1 to A14 in accordance with the invention, particularly any of the particularly preferred compounds A1.001 to A14.003 summarized in Tables 1 to 14, may be used as such, or may be used as starting compounds for further compounds or may be used in combination with inhibitors of DP IV and with inhibitors of analogous enzymes for a therapy of diseases accompanied by an excessive immune response (autoimmune diseases, allergies and transplant rejections), of other chronic-inflammatory diseases, of neuronal diseases and of cerebral damage, of diseases of the skin (inter alia acne and psoriasis), of tumor diseases and of specific virus infections (inter alia SARS).

Furthermore, the invention relates to the use of at least one compound of one of the general formulae A1 to A14 or of at least one of the above-mentioned pharmaceutical or cosmetic compositions for manufacturing a medicament for inhibiting the activity of alanyl aminopeptidases or of analogous enzymes, alone or in combination with inhibitors of DP IV or of analogous enzymes.

Furthermore, the invention relates to the use of at least one compound of one of the general formulae A1 to A14 or of at least one of the above-mentioned pharmaceutical or cosmetic compositions for manufacturing a medicament for topically influencing the activity of alanyl aminopeptidases or of analogous enzymes, alone or in combination with inhibitors of DP IV or of analogous enzymes.

Furthermore, the invention relates to the use of at least one compound of one of the general formulae A1 to A14 or of at least one of the above-mentioned pharmaceutical or optionally also cosmetic compositions for manufacturing a medicament for a prophylactic and therapeutic treatment of a number of diseases claimed, in an exemplifying way, in claims 48 to 60. In particular embodiments, without restricting the invention, the compounds of the general formulae A1 to A14, especially the particularly preferred single compounds A1.001 to A14.003 shown in Tables 1 to 14, may be used, as such or as starting substances for further substances and in combination with inhibitors of DP IV or of analogous enzymes, for manufacturing a medicament for a therapy of diseases associated with an excessive immune response (autoimmune diseases, allergies or transplant rejections), of other chronic-inflammatory diseases, of neuronal diseases and cerebral damage, of skin diseases (inter alia acne and psoriasis), of tumor diseases and of specific virus infections (inter alia SARS).

Moreover, the invention relates to a process for inhibiting the activity of alanyl aminopeptidases and of analogous enzymes, alone or in combination with inhibitors of DP IV and of analogous enzymes, by an administration of at least one compound of the general formulae A1 to A14 or of at least one of the above pharmaceutical or cosmetic compositions in an amount required for an inhibition of the enzymatic activity.

Moreover, the invention relates to a process for topically influencing the activity of alanyl aminopeptidases and of analogous enzymes, alone or in combination with inhibitors of DP IV and of analogous enzymes, by an administration of at least one compound of the general formulae A1 to A14 or of at least one of the above pharmaceutical or cosmetic compositions in an amount required for influencing the enzymatic activity.

Moreover, the invention relates to a process for a prophylaxis and/or therapy of one of the diseases or conditions claimed in the claims 63 to 76 by inhibiting the activity of alanyl aminopeptidases and of analogous enzymes, alone or in combination with inhibitors of DP IV or of analogous enzymes, by an administration of at least one compound of the general formulae A1 to A14 or of at least one of the above pharmaceutical or cosmetic compositions in an amount required for a prophylactic or therapeutic treatment.

The term "analogous enzymes" as used in the present specification and in the claims relates to enzymes having an enzymatic activity analogous to the one shown by the membrane-located alanyl aminopeptidase. This is applicable, for example, for the cytosolic alanyl aminopeptidase. The above term is also explained, in this sense, in the above-referenced textbook "A. J. Barrett et al.; Handbook of Proteolytic Enzymes, Academic Press, 1998".

In the general formulae A1 to A14, as can be seen from claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 and 27 in a general form, the residues Rn, i. e. the residues R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12 and R13, independent of each other represent a residue selected from the group consisting of hydrogen, unsubstituted or substituted, straight chain or branched C_1 - to C_{12} alkyl, C_2- to C_{12} alkenyl and C_2- to C_{12} alkynyl, hydroxy, thiol, C_1 - to C_{12} alkoxy, C_1 - to C_{12} alkylthio, unsubstituted or substituted, uncondensed or condensed aryl and cycloalkyl optionally containing one or several hetero atoms from the group of N, O, P and S, unsubstituted or substituted amino, unsubstituted or substituted carbonyl, unsubstituted or substituted thiocarbonyl and unsubstituted or substituted imino.

In detail, the residues Rn, in embodiments of the invention where they represent unsubstituted straight chain or branched alkyl groups having 1 to 12 carbon atoms, represent in preferred embodiments methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, i-pentyl, sec-pentyl, tert-pentyl, n-hexyl, i-hexyl,

3-methylpentyl, 2-ethylbutyl, 2,2-dimethylbutyl as well as all straight chain and branched isomers for the residues heptyl, octyl, nonyl, decyl, undecyl and dodecyl. In accordance with the invention, particularly preferred from the above-mentioned group are alkyl groups having 1 to 6 carbon atoms; among those, the residues methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and tert-butyl are even more preferred.

In other embodiments according to the invention, the residues Rn, in cases where they represent unsubstituted straight chain or branched alkenyl groups having 2 to 12 carbon atoms, represent in preferred embodiments vinyl, allyl, 1-butenyl, 2-butenyl and all straight chain and branched residues for the radicals pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl and dodecenyl, also with respect to the position of the C=C double bond. In further embodiments of the invention, the residues Rn may also represent straight chain or branched alkenyl groups having several double bonds. Preferred residues of this group are the butadienyl group and the isoprenyl group. Among the above-mentioned groups, particularly preferred in accordance with the invention are the alkenyl groups having 2 to 6 carbon atoms; of those, the groups vinyl, allyl, 1-butenyl and 2-butenyl are even more preferred.

In other embodiments according to the invention, the residues Rn, in cases where they represent unsubstituted straight chain or branched alkynyl groups having 2 to 12 carbon atoms, represent in preferred embodiments ethynyl, propynyl, 1-butynyl, 2-butynyl and all straight chain and branched residues for the radicals pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, undecynyl and dodecynyl, also with respect to the position of the C≡C triple bond. Among the above-mentioned groups, particularly preferred in accordance with the invention are the alkynyl groups having 2 to 6 carbon atoms; of those, the groups ethynyl, propynyl, 1-butynyl and 2-butynyl are even more preferred.

In accordance with the invention, straight chain and branched alkyl, alkenyl and alkynyl residues may be substituted in a further embodiment of the invention. The substituent(s) may be positioned at any desired position of the backbone made of carbon atoms and may be selected from the group consisting of halogen atoms as fluorine, chlorine, bromine and iodine, alkyl groups having 1 to 6 carbon atoms, alkoxy groups having 1 to 6 carbon atoms in the alkyl residue and amino groups which may be unsubstituted or substituted with one or two alkyl residues independently of each other and having 1 to 6 carbon atoms.

In further embodiments of the invention, the residues Rn in the general formulae A1 to A14 represent C_1 - to C_{12} alkoxy residues or C_1 - to C_{12} alkylthio residues. Also for the C_1 - to C_{12} alkyl residues of these alkoxy and alkylthio groups, the above definitions of the straight chain and branched alkyl residues are applicable. Particularly preferred are straight chain C_1 - to C_6 alkoxy groups and straight chain C_1 - to C_6 alkylthio groups, and particularly preferred are the residues methoxy, ethoxy, n-propoxy, methylthio, ethylthio and n-propylthio.

In further embodiments of the invention, the residues Rn in the general formulae A1 to A14 may also represent unsubstituted or substituted cycloalkyl residues. In accordance with the invention, the cycloalkyl residues may preferably contain three to eight atoms in the ring and may consist exclusively of carbon atoms or may contain one or several hetero atom(s). Among the purely carbocyclic rings, the residues cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptenyl, cycloheptadienyl and cycloheptatrienyl are particularly preferred. Examples for hetero atom-containing cycloalkyl residues are, in further embodiments of the invention, the residues tetrahydrofuranyl, pyrrolidinyl, imidazolinidyl, piperidinyl, piperazinyl and morpholinyl. Substituents to these carbocyclic and heterocyclic cycloalkyl residues may be selected from the above group of substituents of linear alkyl groups.

In further embodiments of the invention, the residues Rn in the compounds of the general formulae A1 to A14 may represent uncondensed or condensed aryl residues optionally containing one or several hetero atoms from the group of N, O, P and S. The aryl residues may have one ring or may have several rings and, if having several rings, two rings are preferred. Moreover, one ring may preferably have five, six or seven ring members. In systems consisting of several rings condensed to each other, benzo-condensed rings are particularly preferred, i. e. ring systems wherein at least one of the rings is an aromatic six-membered ring. Particularly preferred are aryl residues purely consisting of carbon atoms, selected from phenyl, cyclopentadienyl, cycloheptatrienyl and naphthyl. Particularly preferred aryl residues containing hetero atoms are, for example, selected from the group consisting of indolyl, cumaronyl, thionaphthenyl, quinolinyl (benzopyridyl), quinazolinyl (benzopyrimidinyl) and quinoxylinyl (benzopyrazinyl).

In another embodiment of the invention, cyclic residues either consisting of one ring or consisting of several rings, either containing carbon atoms exclusively or also containing hetero atoms, either aromatic systems or non-aromatic systems, may be substituted. The substituents may be bound to any position of the ring system, either to a carbon atom or to a hetero atom. They may be selected from the group consisting of halogen atoms as, for example, fluorine, chlorine, bromine and iodine, alkyl groups having 1 to 6 carbon atoms, alkoxy groups having 1 to 6 carbon atoms in the alkyl group, and unsubstituted amino groups or amino groups substituted with one or two alkyl groups having – independent of each other - 1 to 6 alkyl groups.

Moreover, in accordance with the invention, the residues Rn (= R1 to R13) may also represent unsubstituted amino residues (-NH_2) or unsubstituted imino residues (-NH-) or substituted amino residues (-NHR1 or –NR1Rm) or substituted imino residues (>NRm). Herein, the residues R1 and Rm may have the meanings defined above in detail for the residues Rn, and they may be identical or different.

In accordance with the invention, the residues Rn (= R1 to R13) may also represent unsubstituted carbonyl residues (H-(C=O)-) or unsubstituted thiocarbonyl residues (H-(C=S)-) or for substituted carbonyl residues (Rm-(C=O)-) or substituted thiocarbonyl residues (Rm-(C=S)-). In these residues, the substituents Rm of substituted carbonyl residues or substituted thiocarbonyl residues have the meanings defined above for the possible substituents of the residues Rn.

In accordance with the invention, the above-mentioned residues Rn (= R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12 and/or R13) may be bound to the respective basic structures of the general formulae A1 to A14 via one of their carbon atoms. In an alternative embodiment, it is also possible that the residues Rn are bound to the respective basic structures of the general formulae A1 to A14 via the hetero atom or via one of their hetero atoms.

In several of the general formulae A1 to A14 (for example in the general formulae A1, A6 (i. e. A6a, A6b and A6c), A8 and A14), Y, Y1 and Y2 represent residues bound to the basic structure of the respective formula via a C=Y double bond (or a C=Y1 double bond and/or a C=Y2 double bond). In the formulae where they appear, the groups Y represent – independent of each other – one of the residues O, S or NRn, for example NR3, NR4 or NR5, bound to a carbon atom via a double bond. In the latter residues, the radicals Rn (for example R3, R4, R5) may have the meanings mentioned above, including the meaning "hydrogen". Particularly preferably, Y represents O bound to a carbon atom via a double bond.

In several of the general formulae A1 to A14 (for example in the formulae A3, A9, A12, A14), X, X1, X2 and Z represent residues bound to two different carbon atoms via a C-X single bond each (or via a C-X1 single bond or via a C-X2 single bond) or via a C-Z single bond each. In the general formulae where they appear, the residues X and Z represent – independent of each other – the residues >NH, >NRn (for example >NR5 or >NR10), -O-, -S- $-CH_2-$, -CHRn- or $-CRn_2-$, bound to

two different carbon atoms by a single bond each, wherein the residues Rn have the meaning given above, or they represent the residues >N-, >CH- or >CRn- (for example >CR8- or >CR9-) bound to three different carbon atoms via a single bond each, wherein Rn (for example R8, R9) have the meanings given above.

In the compounds of the general formula A6, Z represents P or S.

In the compounds having the general formulae A8, X and Z independent of each other represent residues from the group consisting of hydroxy, thiol, C_1 - to C_{12} alkoxy, C_1 - to C_{12} alkylthio, unsubstituted or substituted, uncondensed or condensed aryl or cycloalkyl optionally containing one or several hetero atoms from the group of N, O, P and S, and amino (NH_2, NHR1, NR1R2), wherein all above-mentioned meanings of X and Z correspond to the meanings for alkoxy, alkylthio, aryl, cycloalkyl and amino which were defined above in detail for the residues Rn of the general formulae A1 to A14.

In the compounds of the general formula A12, X1 and X2 may be identical or different and – independent of each other – are selected from the group consisting of hydroxy, thiol, C_1 - to C_{12} alkoxy, C_1 - to C_{12} alkylthio, unsubstituted or substituted, uncondensed or condensed aryl or cycloalkyl optionally containing one or several hetero atoms from the group of N, O, P and S, hydroxyl, thiol and amino (NH_2, NHR1, NR1R2). Therein, R1 and R2 have the meanings given above.

In the compounds of the general formula A14, X represents N or CH or CR8, P, P=O, $P(OH)_2$, P(OH)(OR8) or P(OR8)(OR9), and Z represents NH, NR10, O or S. In these residues, R8, R9 and R10 have the meanings defined above.

The compounds of the general formulae A1 to A14 (in general) as defined in claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 and 27 and the compounds

A1.001 to A14.007 in Tables 1 to 14 in the claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and 28 (specifically) may be prepared in accordance with processes known from the literature or are commercially available.

The compounds corresponding to the general formulae A1 to A14 (in general) and the specific compounds A1.001 to A14.003 indicated in Tables 1 to 14 (in preferred embodiments of the invention) are claimed for a use in the medical field. The term "for a use in the medical field" is understood here, and in the claims as well, in its broadest sense and relates to all conceivable fields of application, where the compounds of the general formulae A1 to A14 defined by the present invention, and the compounds A1.001 to A14.003 as mentioned in Tables 1 to 14, in preferred embodiments, may exert an effect in connection to medically relevant conditions of the body of a mammal, in particular of the body of a human.

In connection to such medically relevant conditions, the compounds of the general formulae A1 to A14 (in general) and the preferred compounds A1.001 to A14.003 according to Tables 1 to 14 are used either in the form of a single compound or are used in the form of more than one compound, or several compounds, of the general formulae A1 to A14 (in particular of the compounds A1.001 to A14.003 according to Tables 1 to 14). Also covered by the scope of the present invention is a use of one or more than one compound of the general formulae A1 to A14, preferably of one or more than one compound selected from the group consisting of the compounds A1.001 to A14.003 according to Tables 1 to 14, in combination with other effective agents, for example one or more than one compound having an effect in the inhibition of alanyl aminopeptidases or of analogous enzymes (i. e. of enzymes having an equal substrate specificity) and/or having an effect in the inhibition of other enzymes, e. g. of dopeptidyl peptidase IV (DP IV) or of analogous enzymes (i. e. of enzymes having an equal substrate specificity). Examples of such compounds having an effect as enzyme inhibitor(s) are mentioned in parallel patent applications filed by the Applicants of the present application on the same filing

date as the present application as well as in the Applicants' patent applications referred to in the introduction to the present description, the whole disclosed content of which applications is incorporated into the present specification by this reference.

Specific examples of inhibitors effective as inhibitors of dipeptidyl peptidase IV or of analogous enzymes, which are known from the prior art and may optionally be used together with the compounds of the present invention particularly with one or several of the compounds A1.001 to A14.003 according to Tables 1 to 14, include, for example: Xaa-Pro dipeptides, corresponding derivatives, preferably dipeptide phosphonic acid diaryl esters, dipeptide boronic acids (e. g. Pro-bobo-Pro) and their salts, Xaa-Xaa-(Trp)-Pro-(Xaa)n peptides (n = 0 to 10), corresponding derivatives and their salts, and amino acid (Xaa) amides, corresponding derivatives and their salts, wherein Xaa is an α-amino acid/imino acid or an α-amino acid derivative/imino acid derivative, preferably N^{ε}-4-nitrobenzyl-oxycarbonyl-L-lysine, L-proline, L-tryptophane, L-isoleucine, L-valine, and cyclic amines as, for example pyrrolidine, piperidine, thiazolidine and their derivatives act as the amide structure. Such compounds and their preparation were described in an earlier patent (K. Neubert et al.; DD 29 60 75 A5). Furthermore, tryptophane-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives (TSL) and (2S,2S′,2S′′)-2-[2′-[2′′-amino-3′′-(indol-3′′′-yl)-1′′-oxoprolyl]-1′,2′,3′,4′-tetrahydro-6′8′-dihydroxy-7-methoxyisoquinol-3-yl-carbonyl-amino]-4-hydrome-thyl-5-hydropentanoic acid (TMC-2A) may advantageously be used as the effectors for the DP IV together with the compounds of the general formulae A1 to A14. One example of an inhibitor of DP IV preferably useable together with the compounds of the general formulae A1 to A14 is Lys[$Z(NO_2)$] thiazolidide, wherein Lys represents an L-lysine residue an $Z(NO_2)$ represents 4-nitrobenzyl-oxycarbonyl (see also DD 29 60 75 A5).

Specific examples of inhibitors effective as inhibitors of alalyl aminopeptidase, which are known from the prior art and may optionally be used together with the

compounds of the present invention particularly with one or several of the compounds A1.001 to A14.003 according to Tables 1 to 14, include, for example: actinonine, leuhistine, phebestine, amastatine, bestatine, probestine, β-amino thiols, α-amino phosphinic acids, α-amino phosphinic acid derivatives, preferably D-Phe-ψ-[PO(OH)-CH_2]-Phe-Phe. Known alanyl aminopeptidase inhibitors particularly preferred and useable together with the compounds of the present invention are bestatine (Ubenimex), actinonine, probestine, phebestine, RB3014 or leuhistine.

Another embodiment of the present invention relates to pharmaceutical compositions, which comprise at least one, optionally two or even more, compound(s) of the general formulae A1 to A14, particularly preferably selected from the compounds A1.001 to A14.003 according to Tables 1 to 14. Such pharmaceutical compositions comprise one or several of said compounds in such amounts required for exerting a pharmaceutical effect. Such amounts may in detail be determined by a skilled person by a few routine tests and without adding an inventive activity. In general, these amounts are in ranges of from 0.01 to 1000 mg of each of the compounds of the general formulae A1 to A14, particularly preferred of the compounds A1.001 to A14.003 according to Tables 1 to 14, per administration unit, even more preferred in ranges of from 0.1 to 100 mg of each of said compounds per administration unit. Moreover, amounts adjusted to the respective single mammalian organism or human organism may easily be determined by a skilled person, and it may also be provided that a sufficient concentration of the compound(s) to be used may be achieved by an administration of divided or of several administration units.

Another embodiment of the present invention relates to cosmetic compositions, which comprise at least one, optionally two or even more, compound(s) of the general formulae A1 to A14, particularly preferably selected from the com-pounds A1.001 to A14.003 according to Tables 1 to 14. Such cosmetic compo-sitions comprise one or several of said compounds in such amounts required for exerting

a desired effect, for example a cosmetic effect. Such amounts may in detail be determined by a skilled person by a few routine tests and without adding an inventive activity. In general, these amounts are in ranges of from 0.01 to 1000 mg of each of the compounds of the general formulae A1 to A14, particularly preferred of the compounds A1.001 to A14.003 according to Tables 1 to 14, per administration unit, even more preferred in ranges of from 0.1 to 100 mg of each of said compounds per administration unit. Moreover, amounts adjusted to the respective single mammalian organism or human organism may easily be determined by a skilled person, and it may also be provided that a sufficient concentration of the compound(s) to be used may be achieved by an administration of divided or of several administration units.

The one compound or the several compounds according to the present invention or pharmaceutical or cosmetic compositions containing it/them is/are administered simultaneously with known carrier substances and/or auxiliary substances (adjuvants). Such carrier and auxiliary substances are known to a skilled person as such and also with respect to their function and way of application and need no detailed explanation here.

The invention also comprises pharmaceutical compositions which comprise: one or several of the inhibitors of the DP IV or of the inhibitors of enzymes having a DP IV-analogous enzymatic activity and/or of the inhibitors of the APN or of the inhibitors of enzymes having an APN-analogous enzymatic activity in accordance with the prior art, together with one or with several compound(s) of the general formulae A1 to A14, particularly preferably together with one or several compound(s) which are selected from the compounds A1.001 to A14.003 of the Tables 1 to 14, in a spaced apart formulation in combination with known carrier substances, auxiliary substances and/or additives for a simulta-neous or, with respect to the time, immediately successive administration with the aim of a joint effect.

The administration of the compounds of the general formulae A1 to A14 in general and, preferably, of the compounds A1.001 to A14.007 according to Tables 1 to 14 or the administration of pharmaceutical or cosmetic compositions comprising one or several of the above compounds together with usual carrier substances, auxiliary substances and/or additives, is effected, on the one hand, as a topical application in the form of, for example, creams, ointments, pastes, gels, solutions, sprays, liposomes and nanosomes, lotion, "pegylated" formul-ations, degradable (i. e. decomposable under physiological conditions) depot matrices, hydrocolloid dressings, plasters, micro-sponges, prepolymers and similar novel carrier substrates, jet injections and other dermatological bases/vehicles including instillative application, and on the other hand, as a systemic application for an oral, transdermal, intravenous, subcutaneous, intracutaneous, intramuscular or intrathecal application in suitable recipes or in suitable galenic forms.

In accordance with the invention, the compounds of the general formulae A1 to A14 in general, and preferably the compounds A1.001 to A14.003 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used for an inhibition of the activity of the alanyl aminopeptidases or of analogous enzymes, alone or in combination with inhibitors of the dipeptidyl peptidase IV or with inhibitors of analogous enzymes.

In another embodiment, the compounds of the general formulae A1 to A14 in general, and preferably the compounds A1.001 to A14.003 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used for topically influencing the activity of the alanyl aminopeptidases or of analogous enzymes, alone or in combination with inhibitors of the dipeptidyl peptidase IV or with inhibitors of analogous enzymes.

In preferred embodiments of the invention, the compounds of the general formulae A1 to A14 in general, and preferably the compounds A1.001 to A14.003 according to Tables 1 to 14, alone or in combination, or pharma-ceutical or cosmetic compositions comprising one or several of said compounds are used for a prophylaxis and a therapy of diseases as, for example: multiple sclerosis, Morbus Crohn, Colitis ulcerosa and of other autoimmune diseases as well as of inflammatory diseases, of Asthma bronchiale and of other allergic diseases, of skin and mucosa diseases, for example psoriasis, acne, and of dermatologic diseases being accompanied by a hyperproliferation and by changed differentiation states of fibroblasts, of benign fibrosing and sclerosing skin diseases and of malign fibroblastar hyperproliferation states, of acute neuronal diseases as, for example, ischemia-caused cerebral damage after an ischemic or hemorrhagic stroke, craniocerebral trauma, heart arrest, myocardial infarct or as a consequence of heart surgery, of chronic neuronal diseases, for example Morbus Alzheimer, Pick's disease, of the progressive supranuclear palsy, of a corticobasal degeneration, of a frontotemporal dementia, of Morbus Parkinson, particularly of Morbus Parkinson coupled to the chromosome 17, of Morbus Huntington, of disease states caused by prions, and od amyotrophic lateral sclerosis, of artherosclerosis, of arterial inflammations, of a stent restenosis, of chronic obstructive pulmonal diseases (Chronisch Obstruktive Lungenerkrankungen; COPD), of tumors, of metastases, of prostata tumors, of the Heavy Acute Respiratory Syndrome (SARS) and of sepsis and sepsis-like conditions.

In a further preferred embodiment of the invention, the compounds of the general formulae A1 to A14 in general, and preferably the compounds A1.001 to A14.003 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used for a prophylaxis and a therapy of a rejection of transplanted tissues and cells. As an example of such an application, there may be mentioned the use of one or of several of the above-mentioned compounds or of a pharmaceutical composition

containing one or several of the said compounds in connection with allogenic kidney transplants or stem cell trans-plants.

In a further preferred embodiment of the invention, the compounds of the general formulae A1 to A14 in general, and preferably the compounds A1.001 to A14.003 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used for a prophylaxis and a therapy of rejection and inflammation reactions at, or by, medical devices implanted into an organism ("medical devices"). These may comprise, for example, stents, articulation implants (knee joint implants, hip joint implants), bone implants, heart pacemakers, or other implants. In a further preferred embodiment of the invention, the compounds of the general formulae A1 to A14 in general, and preferably the compounds A1.001 to A14.003 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used in such a way that the compound(s) or composition(s) is/are applied onto the article or articles in the form of a coating or layer, or at least one of the compounds or compositions is admixed, as a substance, to the material of the article or articles. Also in this case, it is possible – of course – that at least one of the compounds or compositions is administered locally or systemically, optionally successively or parallel in time.

In a similar way as described above, and for similar purposes or for the prophylaxis and therapy of the above diseases and conditions mentioned as examples, however without any restriction, the compounds of the general formulae A1 to A14 in general, and preferably the compounds A1.001 to A14.003 according to Tables 1 to 14, alone or in combination, or the above- mentioned pharmaceutical or cosmetic compositions comprising one or several of said above-mentioned compounds may be used for the preparation of a medicament for a prophylaxis and a therapy of the above-mentioned diseases or conditions. These medicaments

may comprise said compounds in the amounts specified above, optionally together with known carrier substances, auxiliary substances and/or additives.

Finally, the invention also relates to a process for inhibiting the activity of alanyl aminopeptidases and of analogous enzymes, alone or in combination with inhibitors of the DP IV and of analogous enzymes by an administration of at least one compound or pharmaceutical or cosmetic composition according to the above detailed description in an amount required for an inhibition of the enzyme activity. The amounts of one of the compounds of the general formulae A1 to A14 in general and of the compounds A1.001 to A14.003 according to Tables 1 to 14 are – as indicated above – in the range of from 0.01 to 1000 mg of one compound per administration unit, preferably in the range of from 0.1 to 100 mg of one compound per administration unit.

The invention also relates to a process for topically influencing the activity of alanyl aminopeptidases and of analogous enzymes, alone or in combination with inhibitors of the DP IV or of analogous enzymes by an administration of at least one compound or pharmaceutical or cosmetic composition according to the above detailed description in an amount required for topically influencing the enzyme activity. Also in these cases, the amounts of said compound(s) are in the above-indicated range.

Furthermore, the invention also relates to a process for the prophylaxis and therapy of a plurality of diseases, for example diseases accompanied by an excessive immune response (autoimmune diseases, allergies, transplant rejections), of other chronically inflammatory diseases, of neuronal diseases and cerebral damage, of skin diseases (inter alia acne and psoriasis), of tumor diseases and of specific virus diseases (inter alia SARS), and particularly of the diseases mentioned above in detail, by an administration of at least one compound or of a pharmaceutical or cosmetic composition in accordance with the above

detailed description in an amount required for the prophylaxis and therapy of the respective disease. Also in these cases, the amounts of the above compound(s) are in the above-mentioned range of from 0.01 to 1000 mg of one compound per administration unit, preferably in the range of from 0.1 to 100 mg of one compound per administration unit.

In the following, the invention is in more detail explained by specific preferred exemplary embodiments. Those exemplary embodiments, however, do not serve a limitation of the invention, but only an exemplifying explanation.

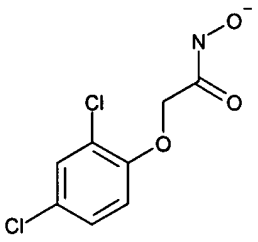
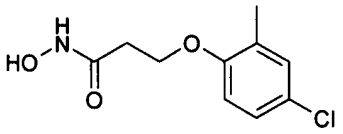
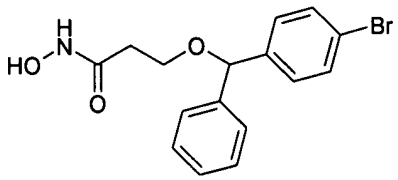
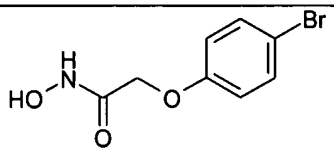
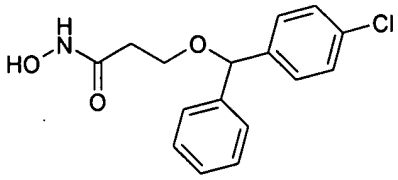
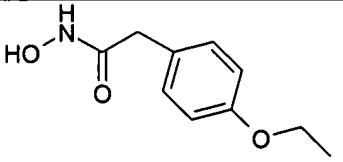
Examples

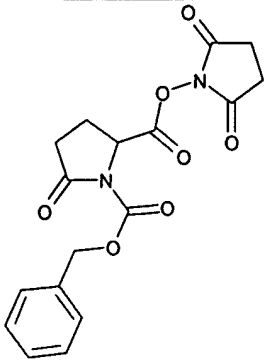
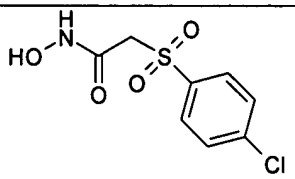
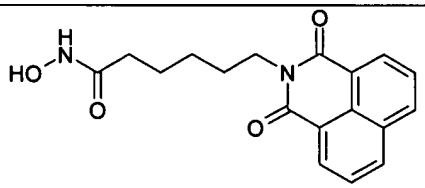
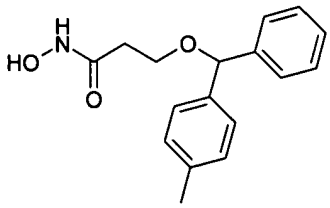
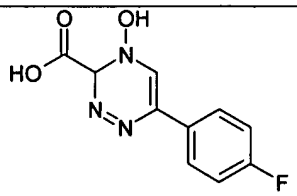
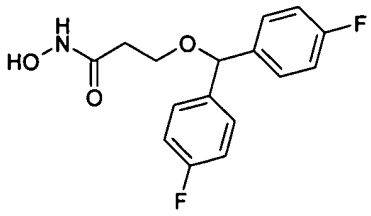
Example 1: Inhibition characteristics of the novel inhibitors of the alanyl aminopeptidases

In the following Tables 1 to 14, novel inhibitors are summarized, for which the inventors could show that these substances are capable of inhibiting alanyl aminopeptidases and enzymes having an analog effect in their enzymatic activity. The inhibition characteristics measured are referred to as IC-50 values or ID50 values (the latter marked with "*") for said enzyme. The enzymatic activity was determined by means of the fluorogenic substrate/product $(Ala)_2$-rhodamine 110.

P29677.S01

Table 1:

Compound ID.	Structure	$IC50_{APN}$ [µM]
A1.001		0.8
A1.002		5.6
A1.003		6.3
A1.004		6.4
A1.005		7.3
A1.006		7.5

A1.007		8.4
A1.008		11.5
A1.009		14.1
A1.010		14.2
A1.011		17.1
A1.012		21.8

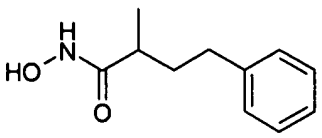
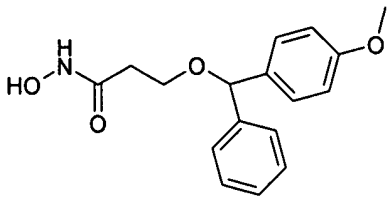
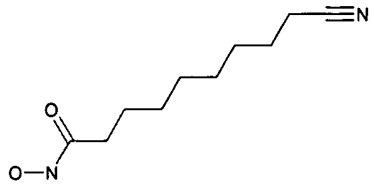
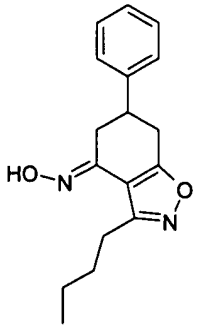
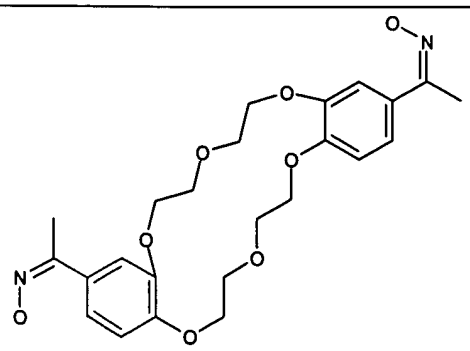
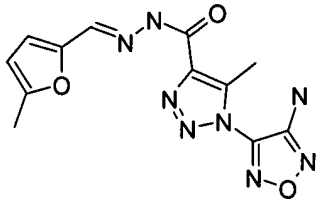
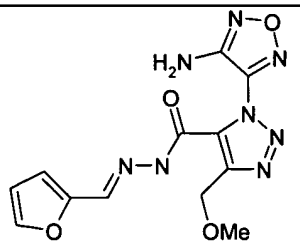
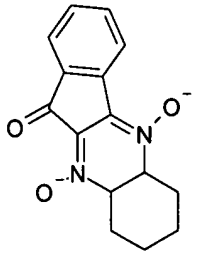
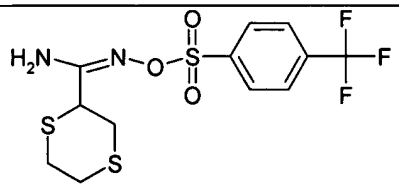
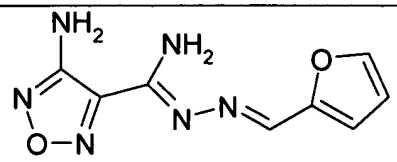
A1.013		25.2
A1.014		33.0
A1.015		80.6

Table 2:

Compound ID.	Structure	$IC50_{APN}$ [µM]
A2.001		2.2

A2.002		8.6
A2.003		10.9
A2.004		12.5
A2.005		13.7
A2.006		13.4
A2.007		14.6

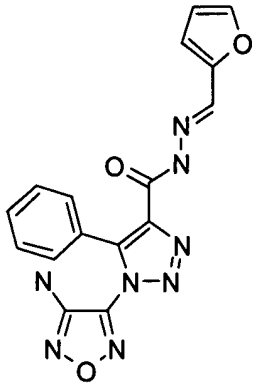
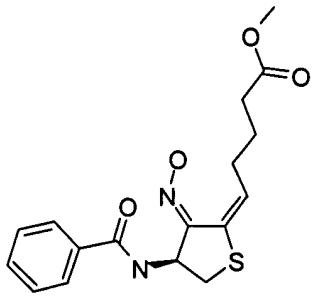
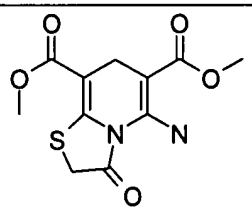
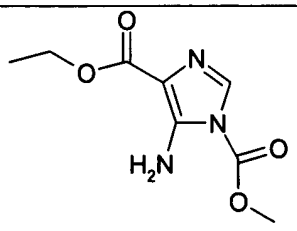
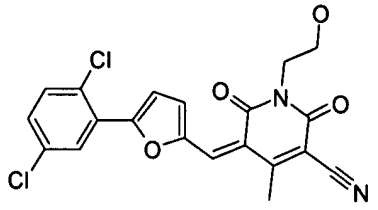
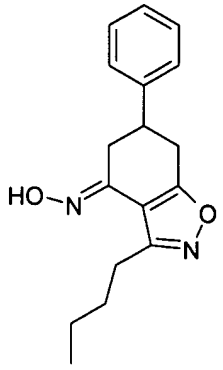
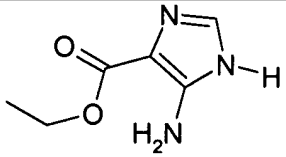
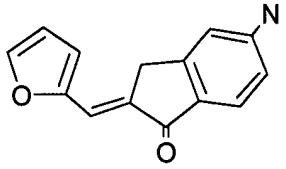
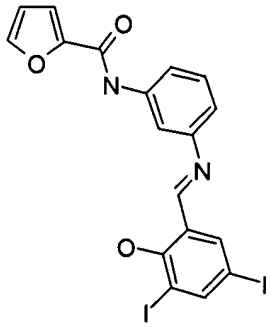
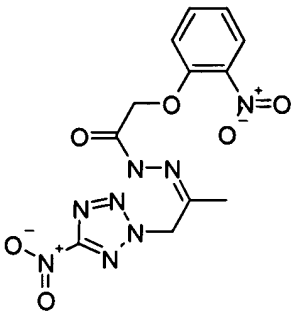
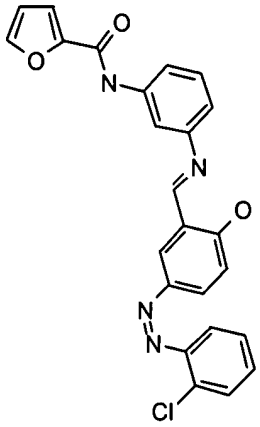
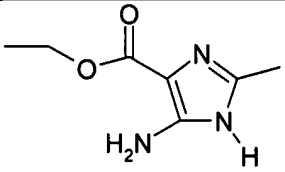
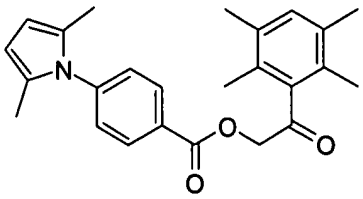
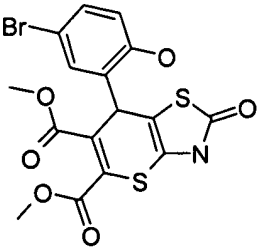
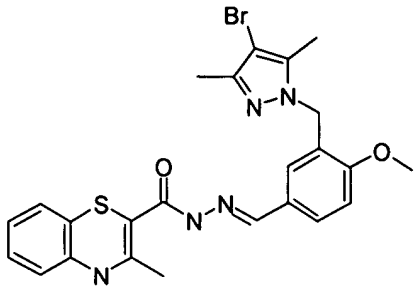
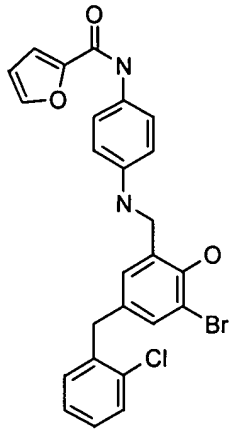
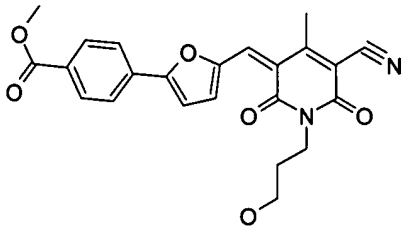
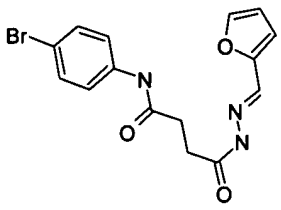
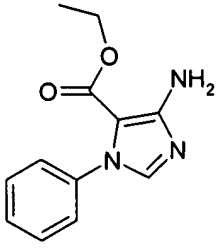
A2.008		46.6
A2.010		93.6

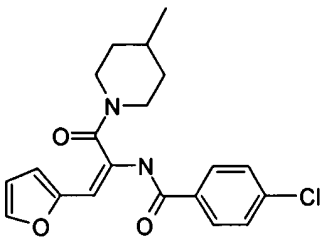
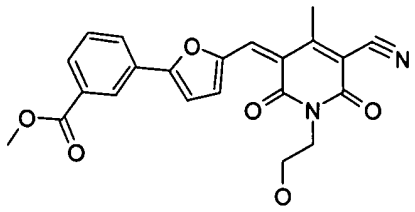
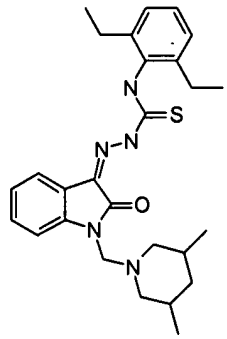
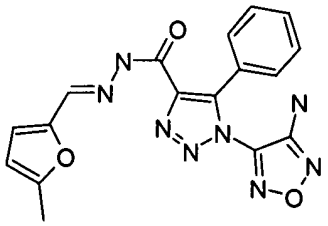
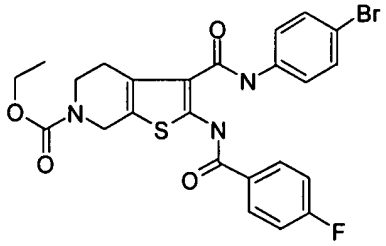
Table 3:

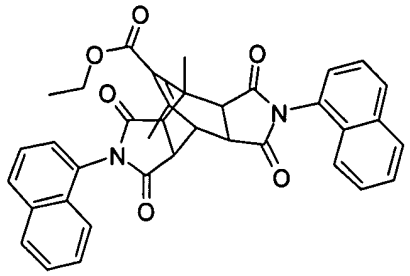
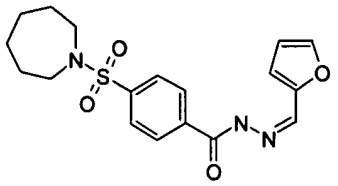
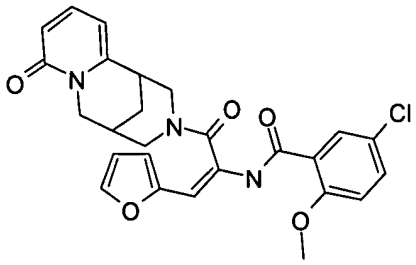
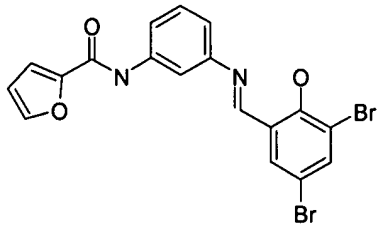
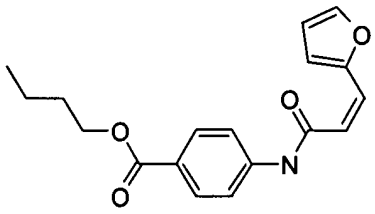
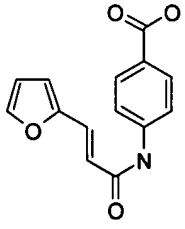
Compound ID.	Structure	$IC50_{APN}$ [µM]
A3.001		" very high active"
A3.002		0.9*

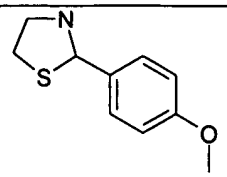
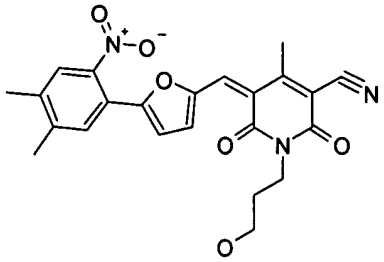
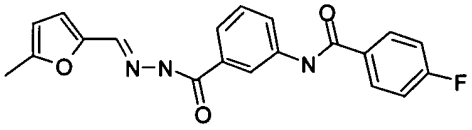
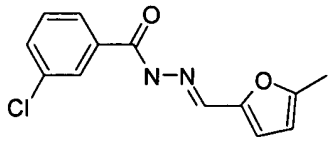
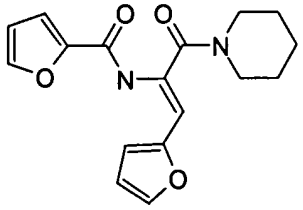
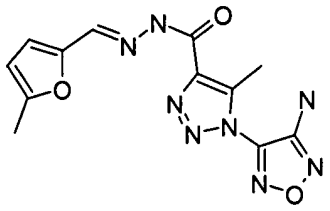
A3.003		1.2*
A3.006		2.2*
A3.007		2.6*
A3.008		2.6*
A3.009		3.0

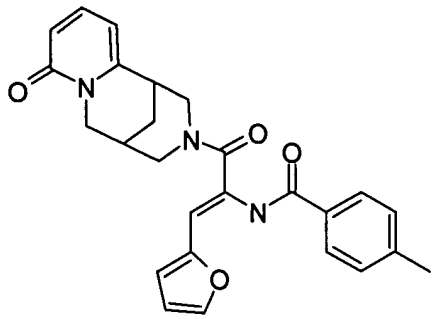
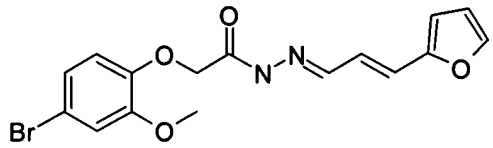
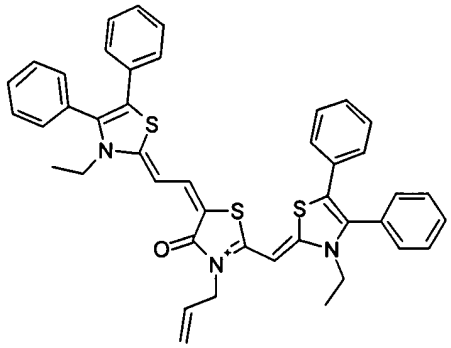
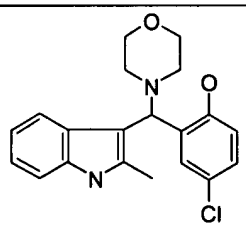
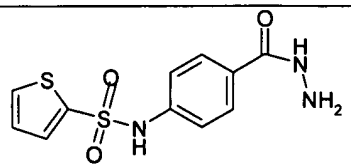
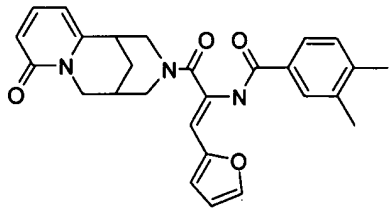
A3.010		3.4
A3.011		3.6
A3.012		4.3
A3.014		4.5
A3.015		4.7

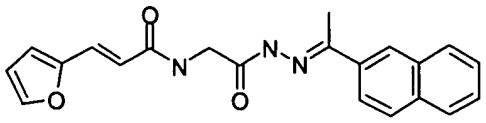
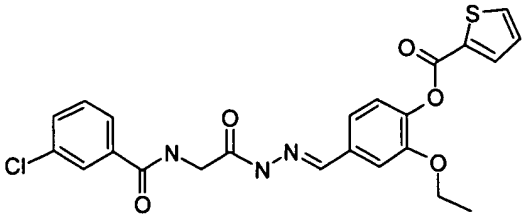
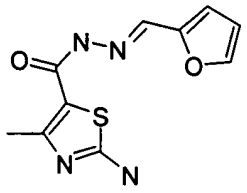
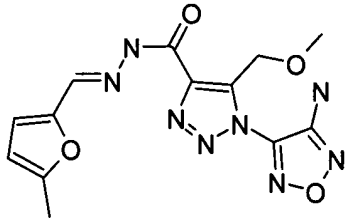
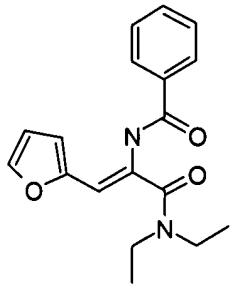
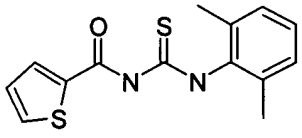
A3.016		4.8
A3.017		4.9
A3.018		5.0
A3.019		5.2
A3.020		5.4

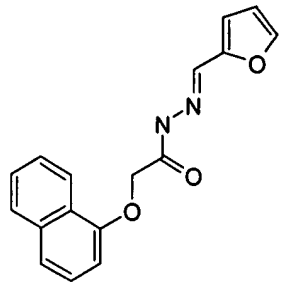
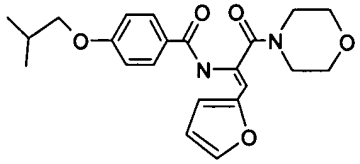
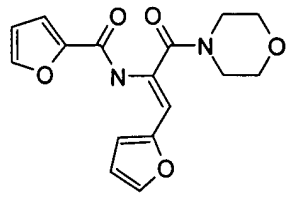
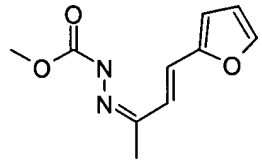
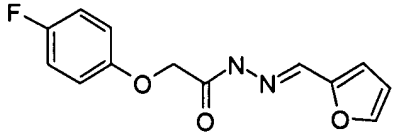
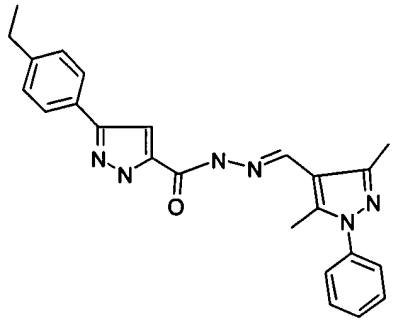
A3.022		6.2
A3.023		6.3
A3.024		6.6
A3.025		6.9
A3.026		7.3

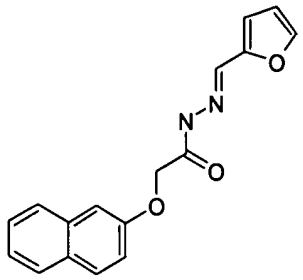
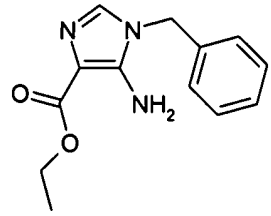
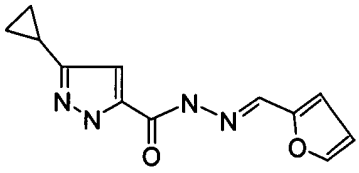
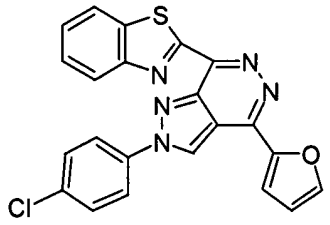
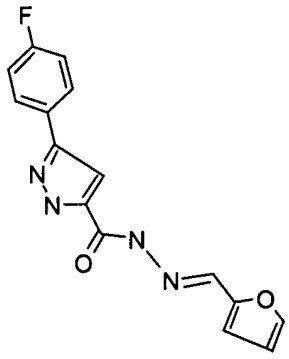
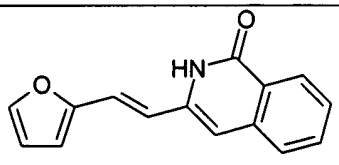
A3.027		7.4
A3.029		8.0
A3.030		8.1
A3.031		8.2
A3.032		8.3
A3.033		8.4

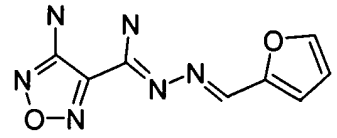
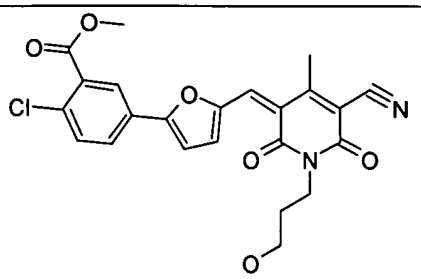
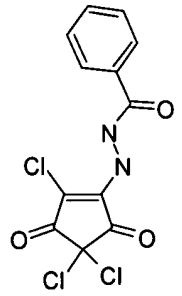
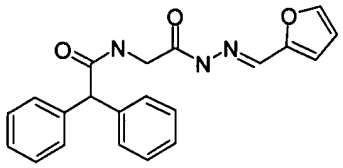
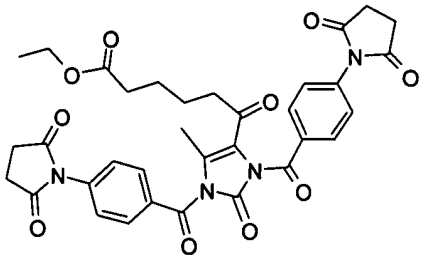
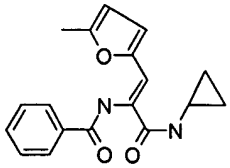
A3.035		9.5
A3.037		9.7
A3.038		9.8
A3.039		10.5
A3.040		10.6
A3.041		10.9

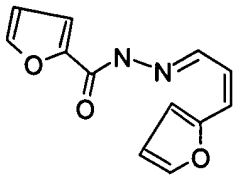
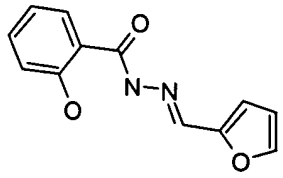
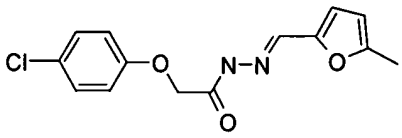
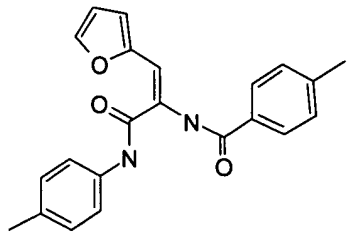
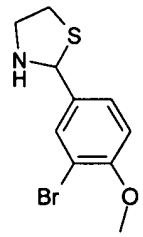
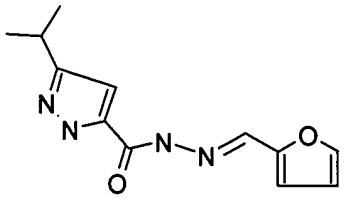
A3.042		11.0
A3.043		11.0
A3.045		11.1
A3.046		11.7
A3.047		11.8
A3.048		11.8

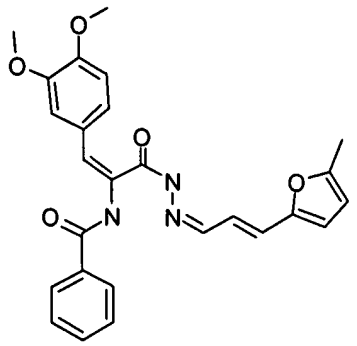
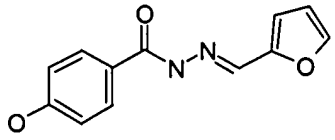
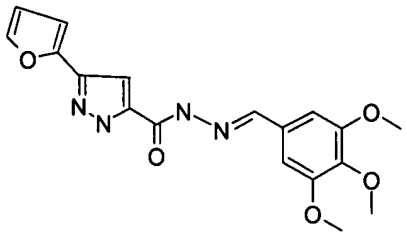
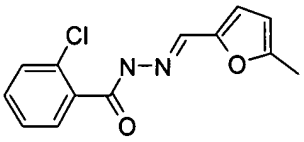
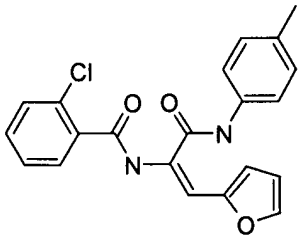
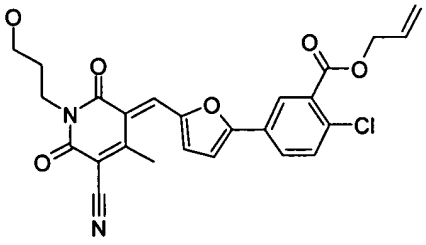
A3.050		12.0
A3.051		12.2
A3.052		12.3
A3.053		12.5
A3.054		12.8
A3.055		12.9

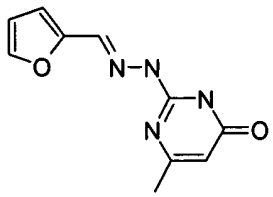
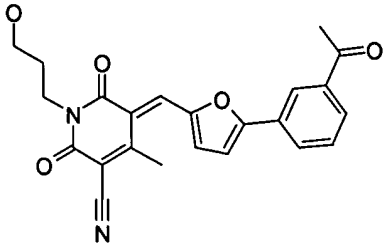
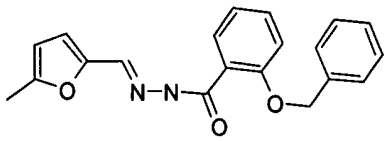
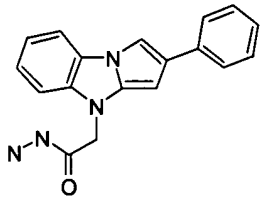
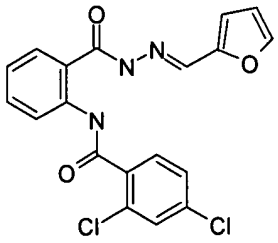
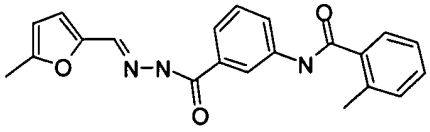
A3.056		12.9
A3.057		13.1
A3.058		13.5
A3.059		13.5
A3.060		13.6
A3.061		13.6

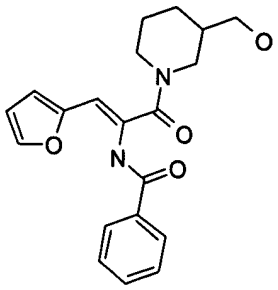
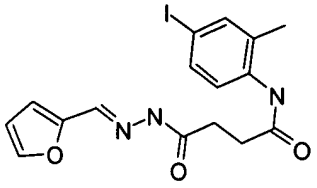
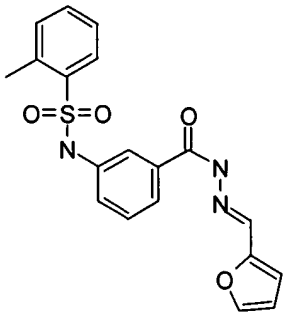
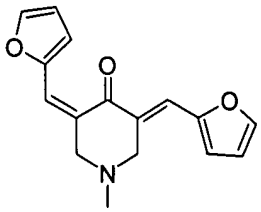
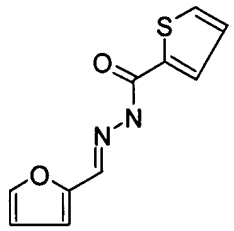
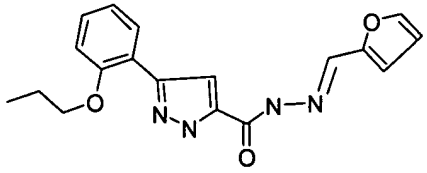
A3.062		13.9
A3.063		14.0
A3.064		14.3
A3.065		14.3
A3.066		14.4
A3.067		14.6

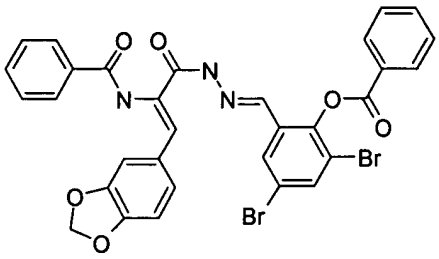
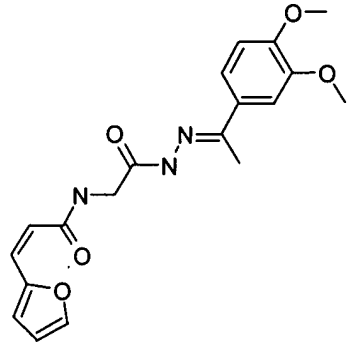
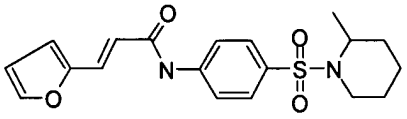
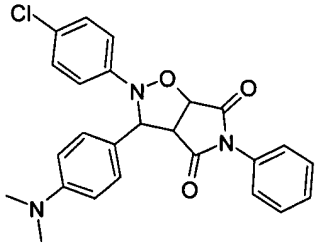
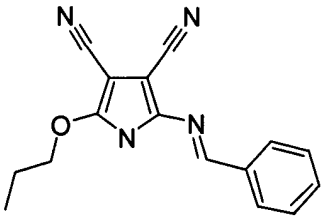
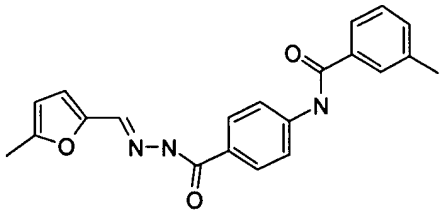
A3.068		14.6
A3.069		15.2
A3.070		15.2
A3.071		15.6
A3.072		15.6
A3.073		15.6

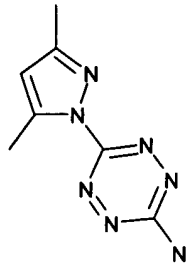
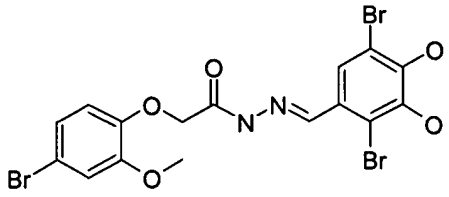
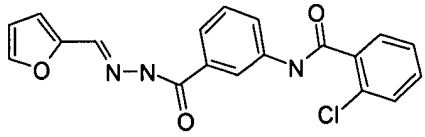
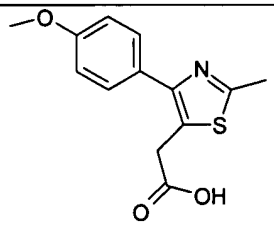
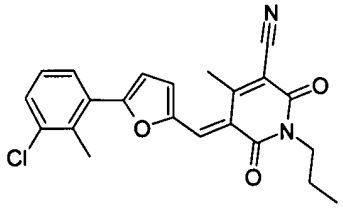
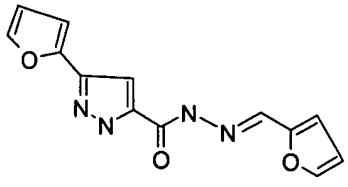
A3.074		16.0
A3.075		16.0
A3.076		16.0
A3.077		16.4
A3.078		16.4
A3.080		16.6

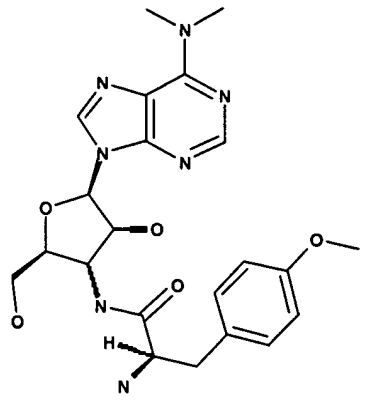
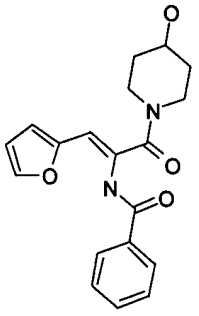
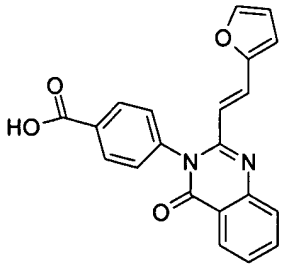
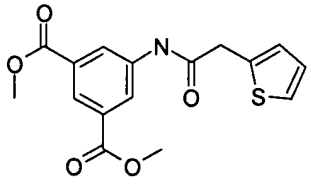
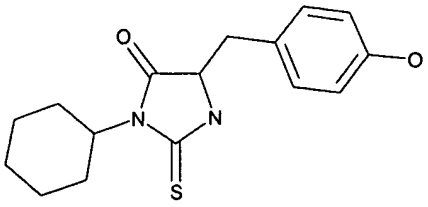
A3.081		16.7
A3.082		16.8
A3.083		17.0
A3.084		17.7
A3.086		17.9
A3.087		18.1

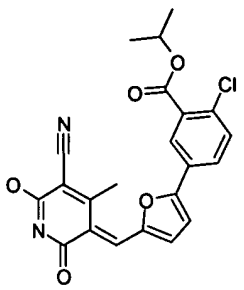
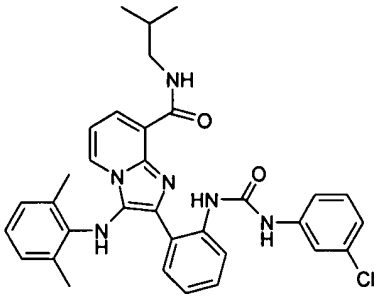
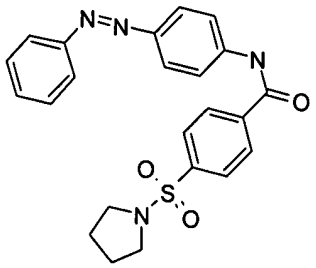
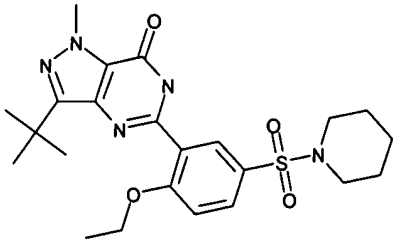
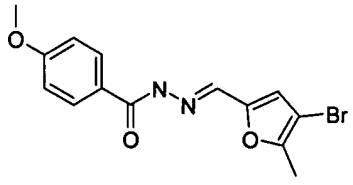
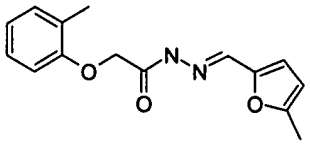
A3.088		18.2
A3.089		18.2
A3.090		18.4
A3.091		18.7
A3.092		18.7
A3.093		18.9

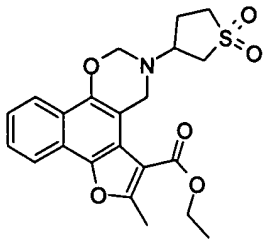
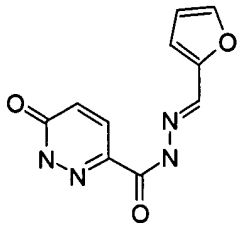
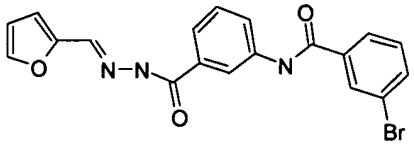
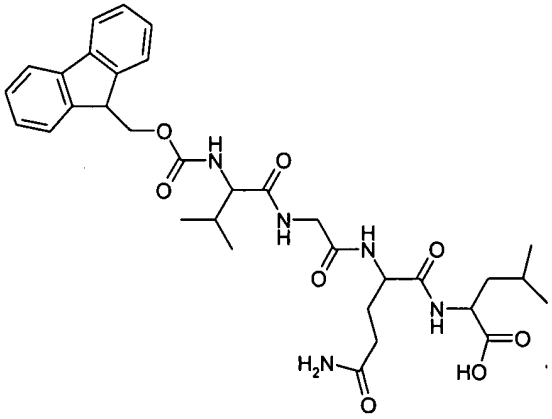
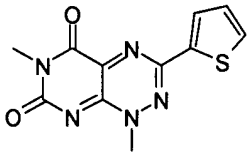
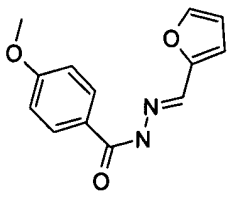
A3.094		19.0
A3.095		9.5
A3.097		19.2
A3.098		19.2
A3.099		19.4
A3.100		19.5

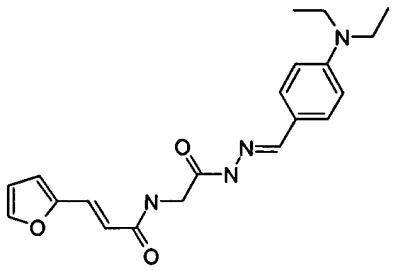
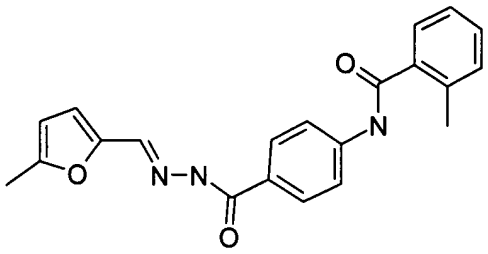
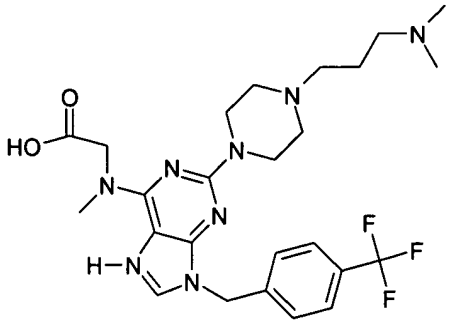
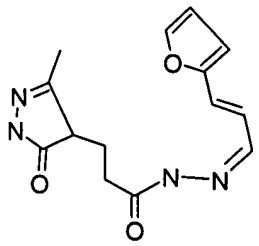
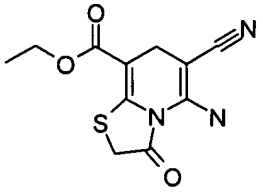
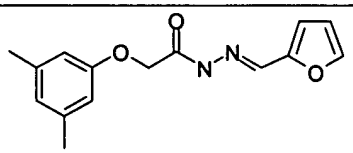
A3.101		19.8
A3.102		19.9
A3.103		19.9
A3.104		20.0
A3.105		20.0
A3.106		20.2

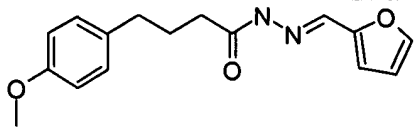
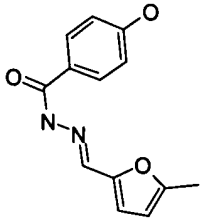
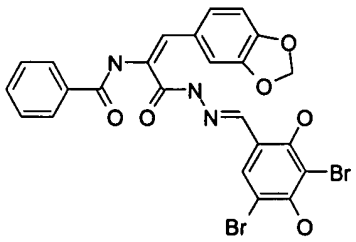
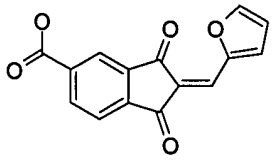
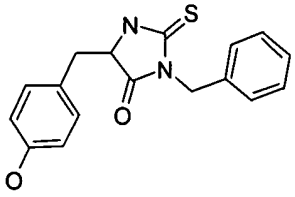
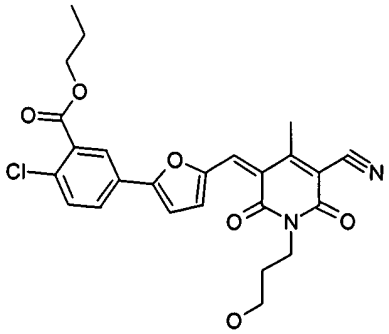
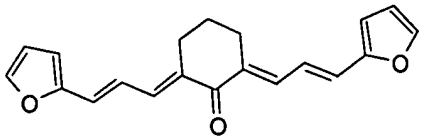
A3.107		20.3
A3.109		20.5
A3.110		20.6
A3.111		20.8
A3.112		20.8
A3.113		20.9

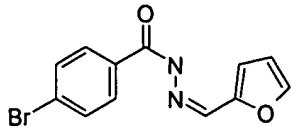
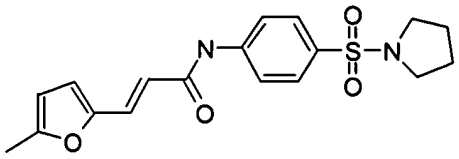
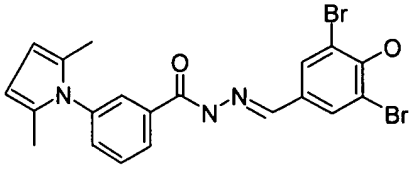
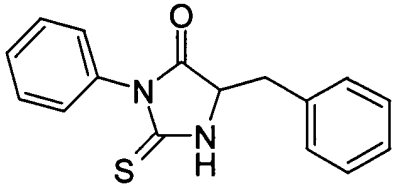
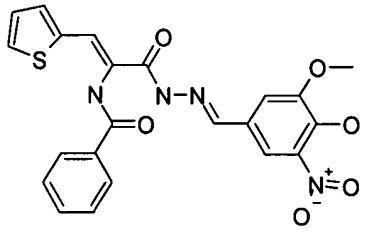
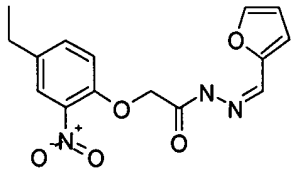
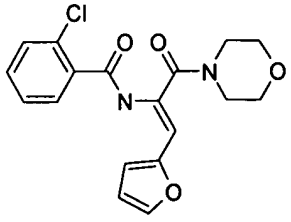
A3.114		20.9
A3.115		21.1
A3.116		21.2
A3.117		21.2
A3.118		21.3

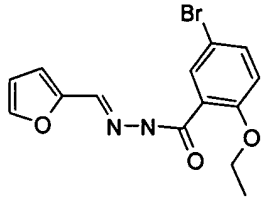
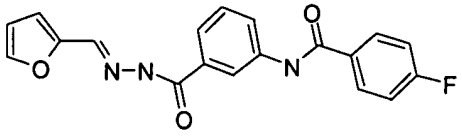
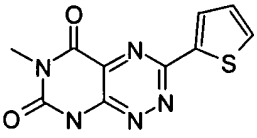
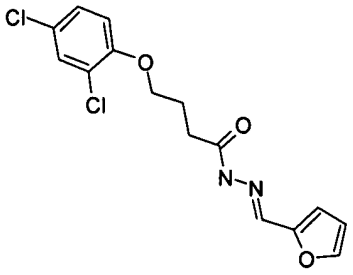
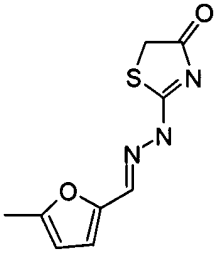
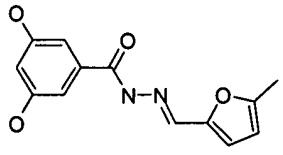
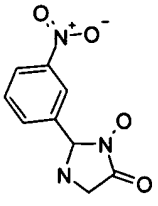
A3.120		21.4
A3.121		21.6
A3.122		21.6
A3.124		21.8
A3.125		21.8
A3.128		22.2

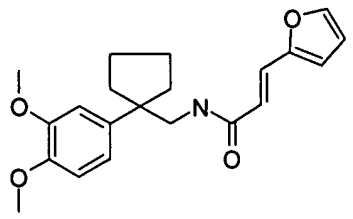
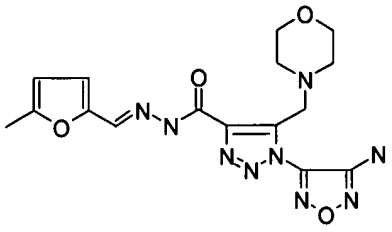
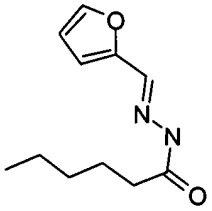
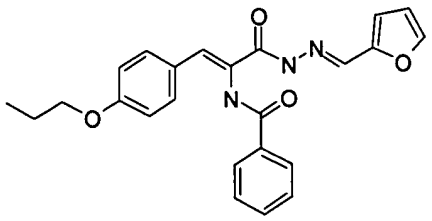
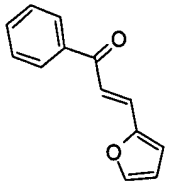
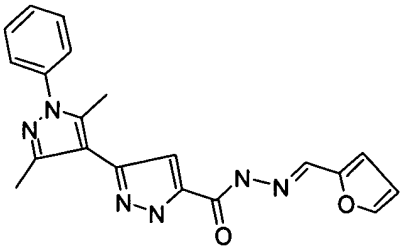
A3.129		22.3
A3.130		22.4
A3.131		22.4
A3.132		22.5
A3.133		25.0
A3.134		22.6

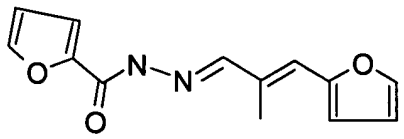
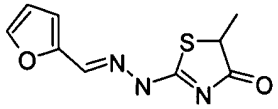
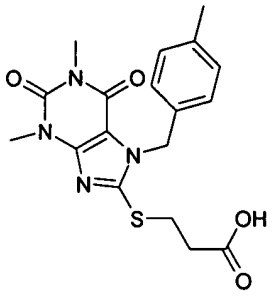
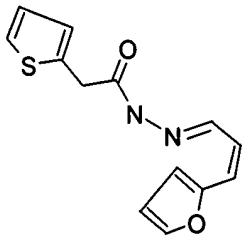
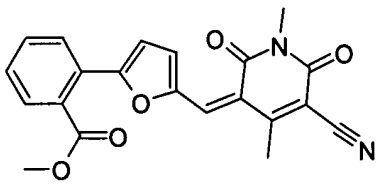
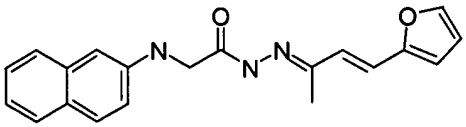
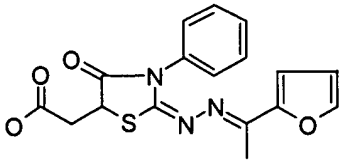
A3.135		22.8
A3.136		22.8
A3.137		23.0
A3.138		23.0
A3.139		23.1
A3.140		23.4

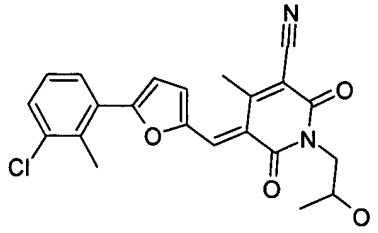
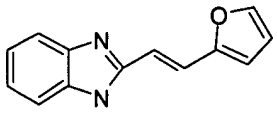
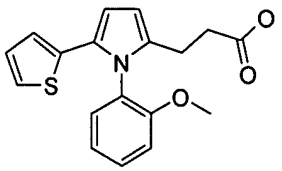
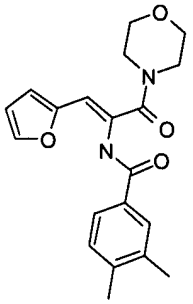
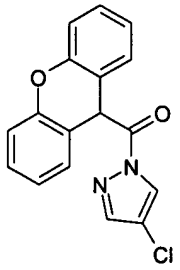
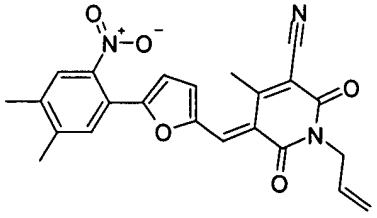
A3.141		23.4
A3.142		23.4
A3.143		23.6
A3.144		23.7
A3.145		23.7*
A3.146		23.8
A3.147		24.4

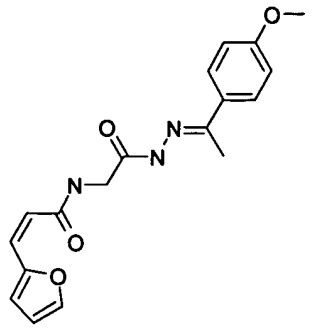
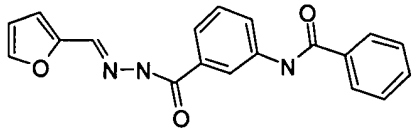
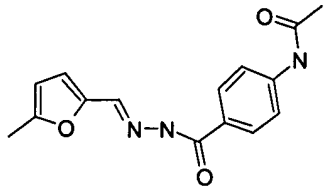
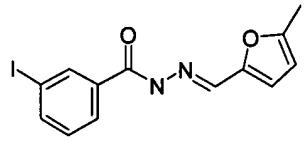
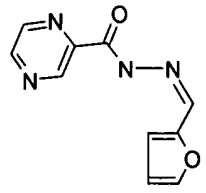
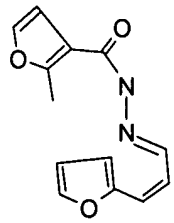
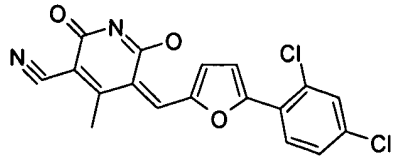
A3.148		24.5
A3.149		24.8
A3.150		24.9
A3.151		26.1
A3.152		25.1
A3.153		25.1
A3.154		25.5

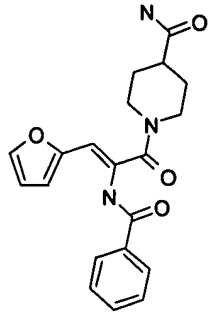
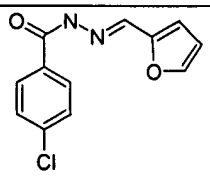
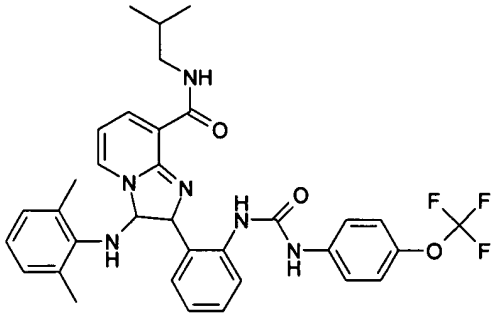
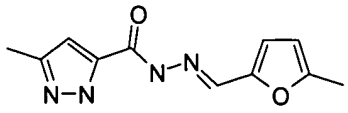
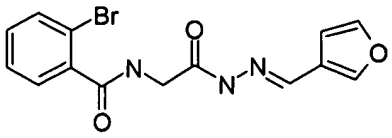
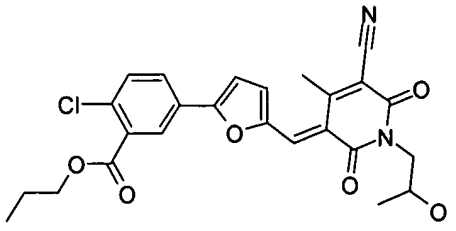
A3.155		25.8
A3.156		25.9
A3.157		26.1
A3.158		26.3
A3.159		22.6
A3.160		26.4
A3.161		26.4

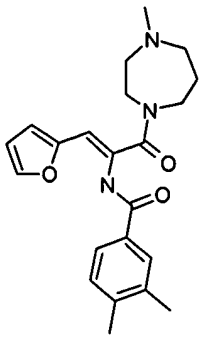
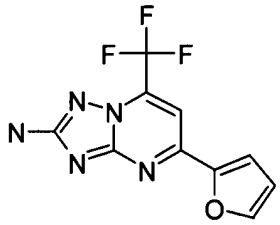
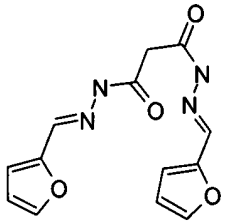
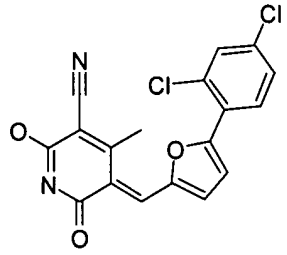
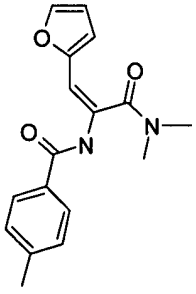
A3.162		26.6
A3.163		26.7
A3.164		26.7
A3.165		27.3
A3.166		27.3
A3.167		27.4

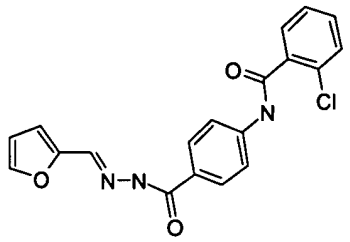
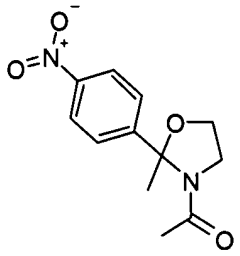
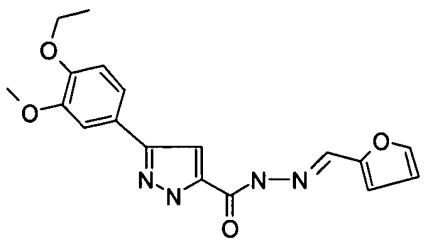
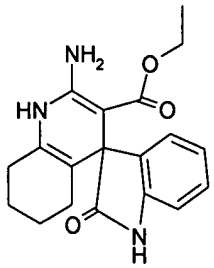
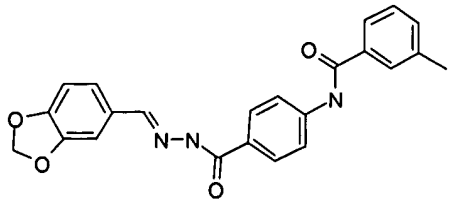
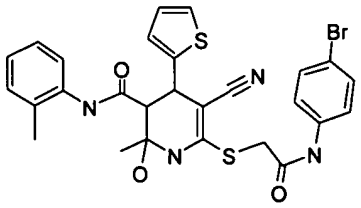
A3.168		27.5
A3.169		27.7
A3.170		28.0
A3.171		28.0
A3.172		28.1
A3.173		28.5
A3.174		28.6

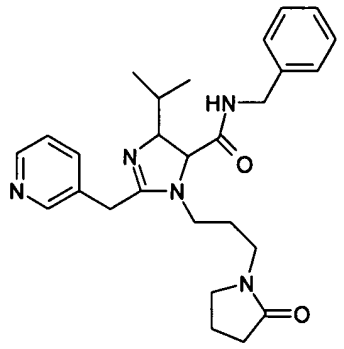
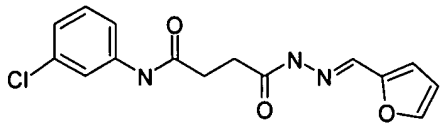
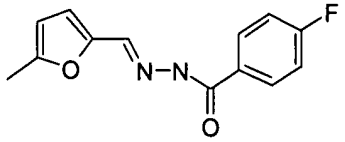
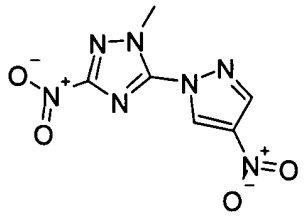
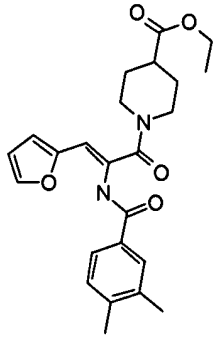
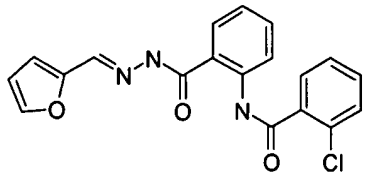
A3.175		28.6
A3.176		28.7
A3.177		28.7
A3.178		28.8
A3.179		29.1
A3.180		29.3

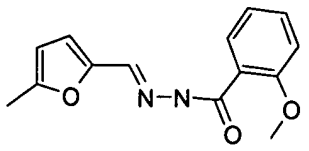
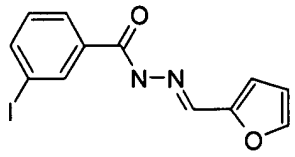
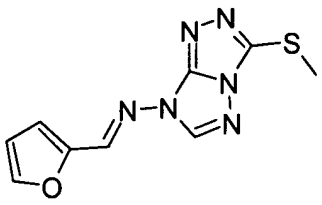
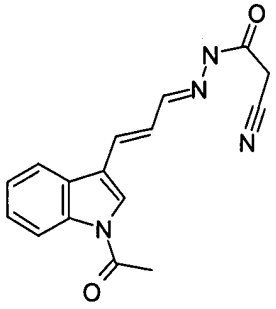
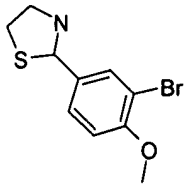
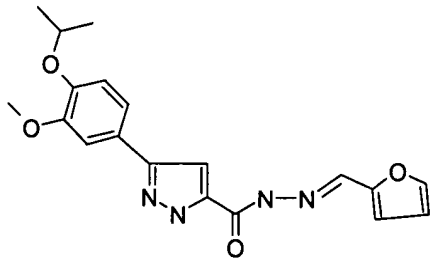
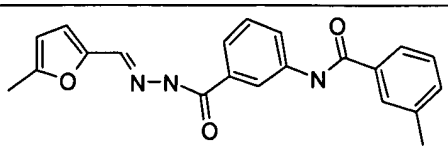
A3.181		29.4
A3.182		29.5
A3.183		29.7
A3.184		30.0
A3.185		30.1
A3.186		30.1
A3.187		30.3

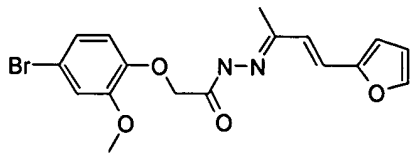
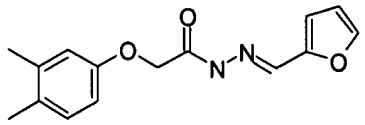
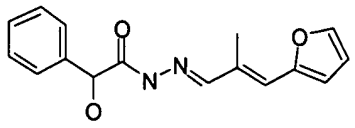
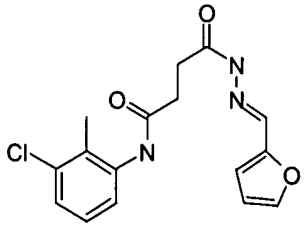
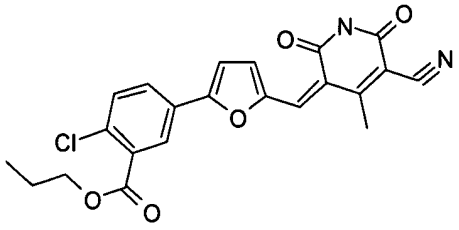
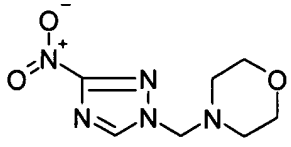
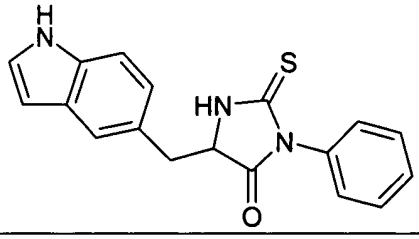
A3.188		30.5
A3.189		30.8
A3.190		31.1
A3.191		31.8
A3.192		31.9
A3.193		32.0

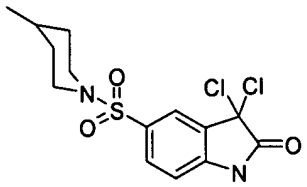
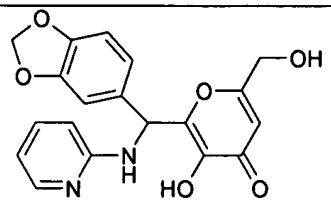
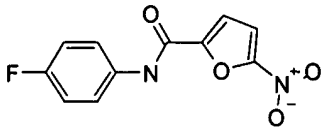
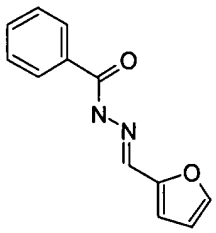
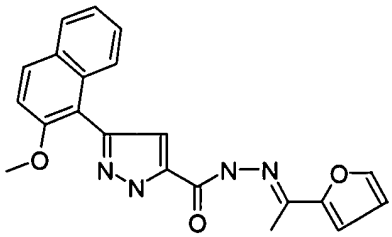
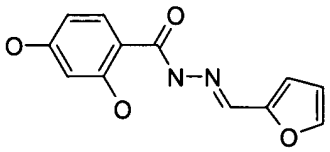
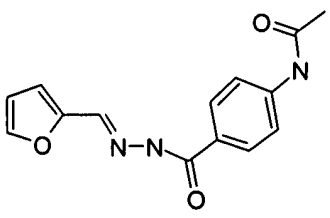
A3.194		32.1
A3.195		32.1
A3.196		32.4
A3.197		32.4
A3.198		32.5

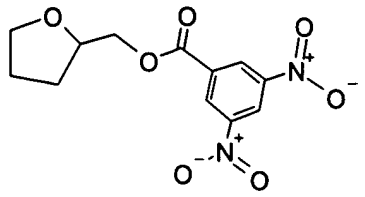
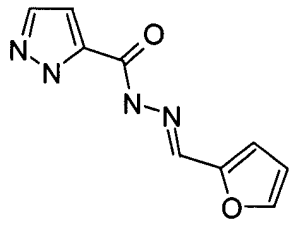
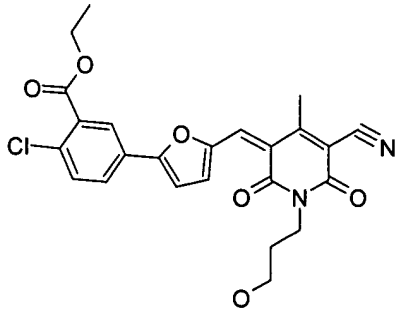
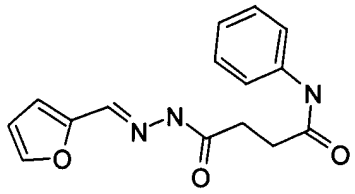
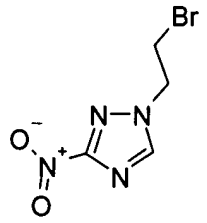
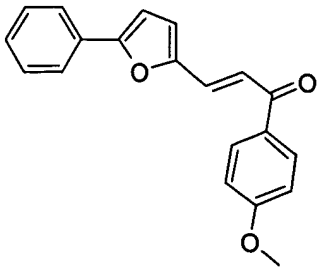
A3.199		32.5
A3.200		32.8
A3.201		33.4
A3.202		33.6
A3.203		33.8*
A3.204		33.9

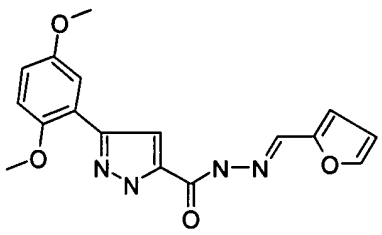
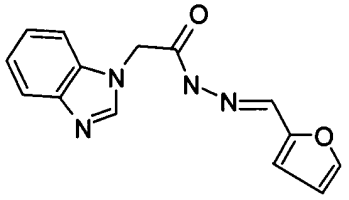
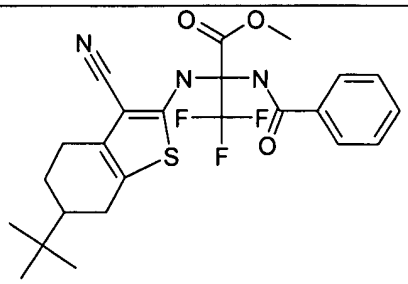
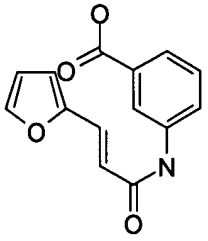
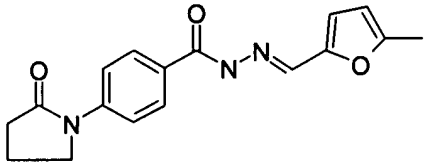
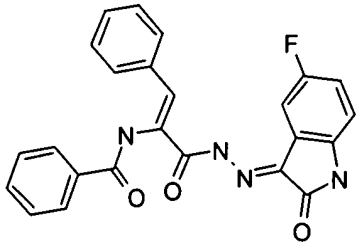
A3.205		34.0
A3.206		34.0
A3.207		34.4
A3.208		34.5
A3.209		34.5
A3.210		34.7

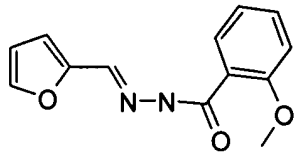
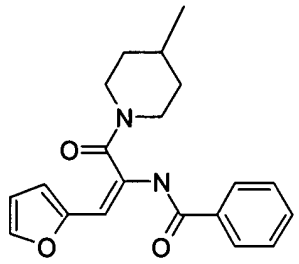
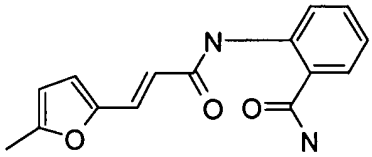
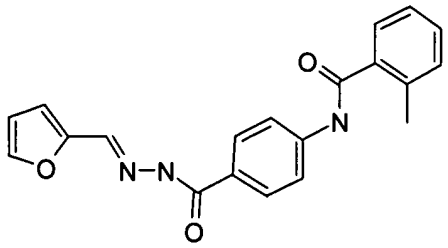
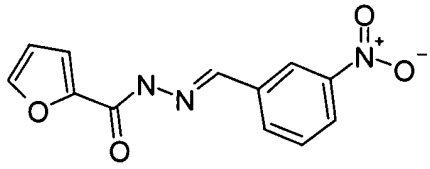
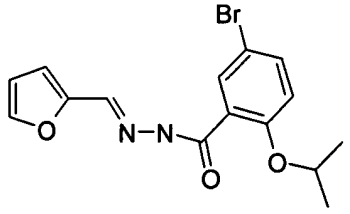
A3.211		34.7
A3.212		34.7
A3.213		34.7
A3.214		35.5
A3.215		35.7
A3.216a		36.1
A3.216b		36.2

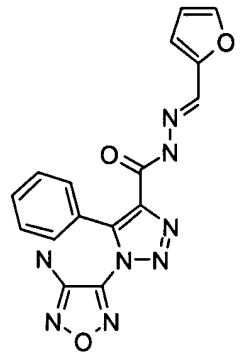
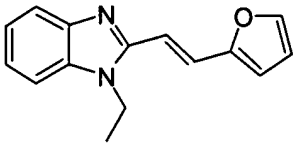
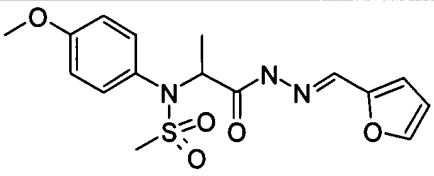
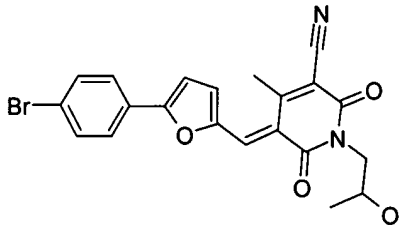
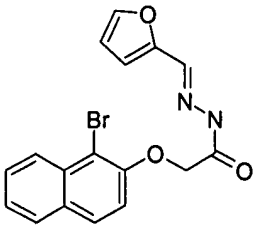
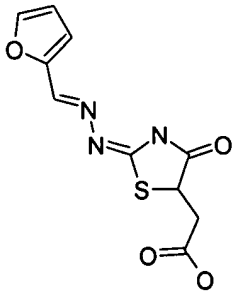
A3.217		36.3
A3.218		36.3
A3.219		36.3
A3.220		36.6
A3.221		36.8
A3.222		36.8
A3.223		36.9

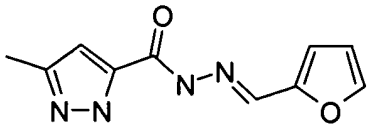
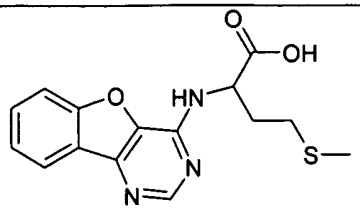
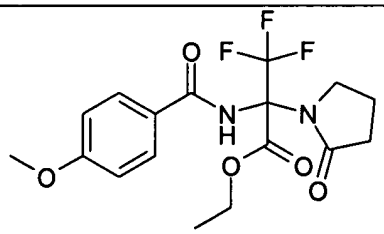
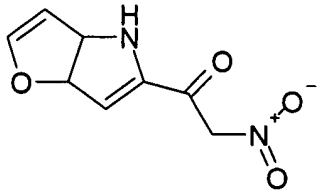
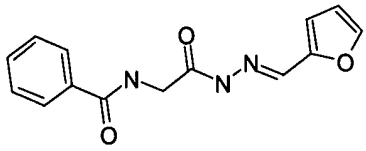
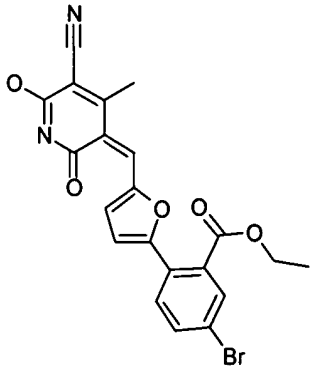
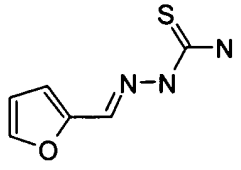
A3.224		37.2
A3.225		37.3
A3.226		37.4
A3.227		37.7
A3.228		38.2
A3.229		38.3
A3.230		38.4

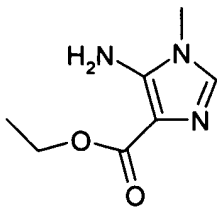
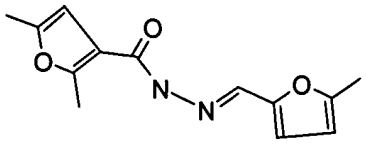
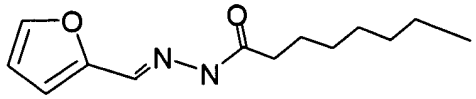
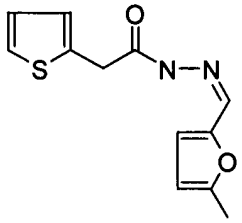
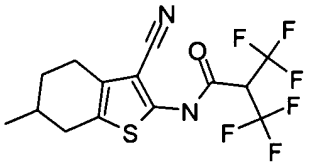
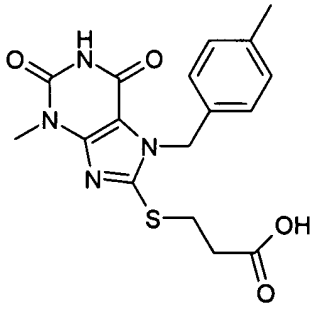
A3.231		39.3
A3.232		40.3
A3.233		41.0
A3.234		41.1
A3.235		41.1
A3.236		41.2

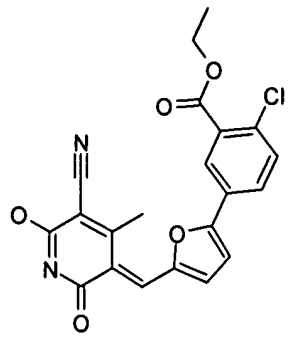
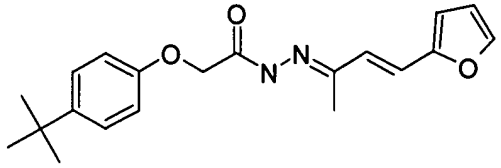
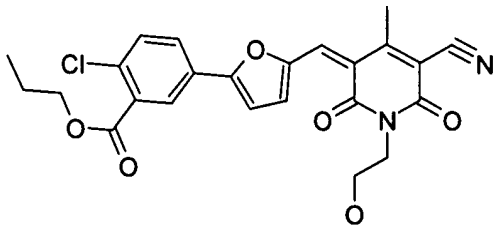
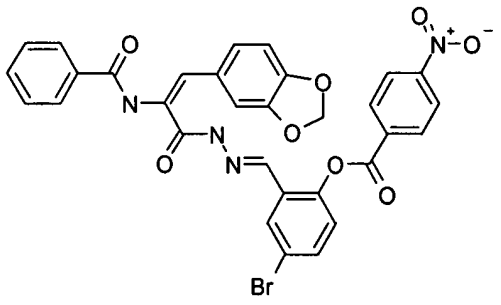
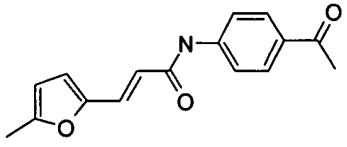
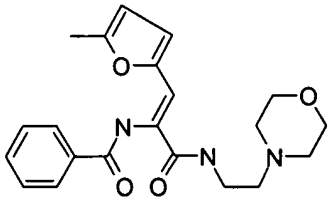
A3.237		43.2
A3.238		43.3
A3.239		43.6
A3.240		44.2
A3.241		44.2
A3.242		44.2

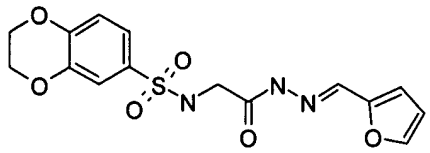
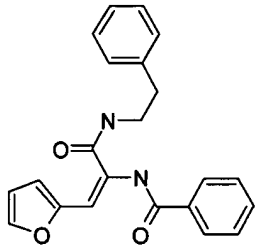
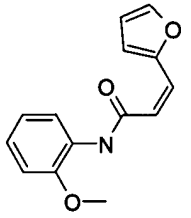
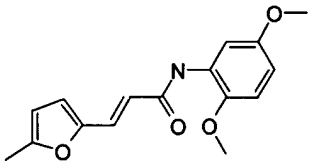
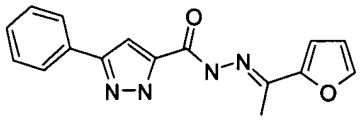
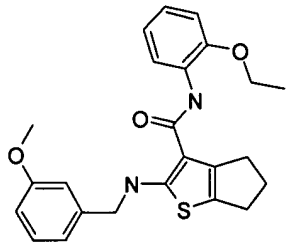
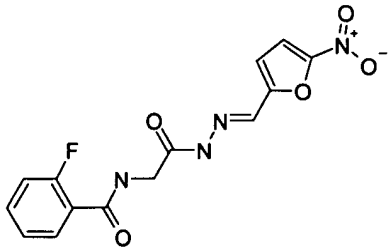
A3.243		44.7
A3.244		45.0
A3.245		45.0
A3.246		45.4
A3.247		45.4
A3.248		46.6

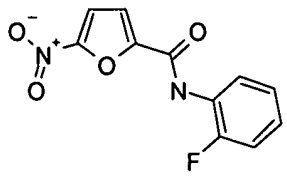
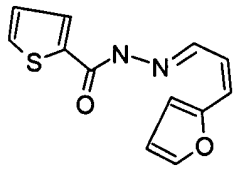
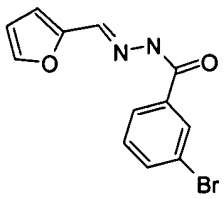
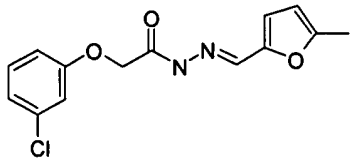
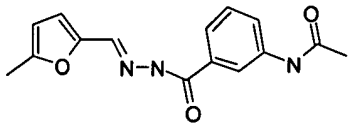
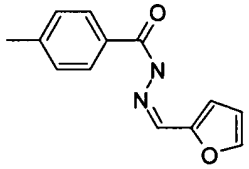
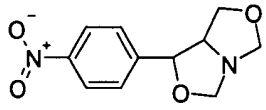
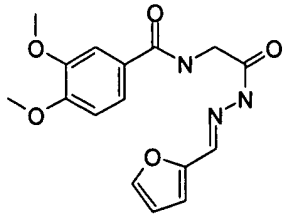
A3.249		46.6
A3.250		46.6
A3.251		47.0
A3.252		47.2*
A3.253		47.3
A3.254		48.1*

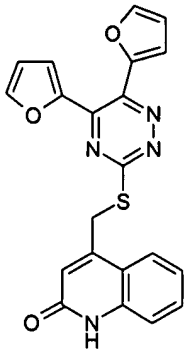
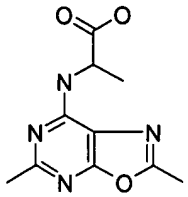
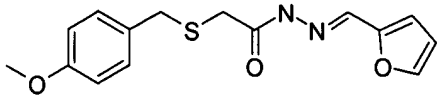
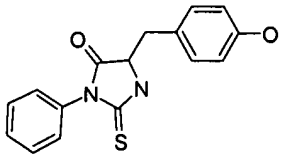
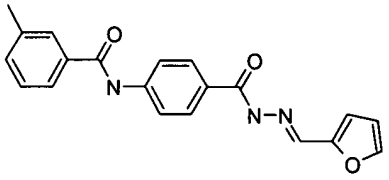
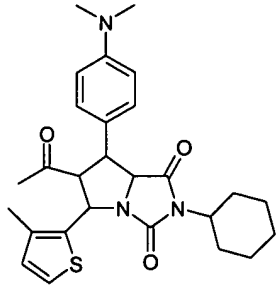
A3.255		48.2
A3.256		48.4
A3.257		48.7
A3.258		49.5
A3.259		49.4*
A3.260		49.9
A3.261		50.0

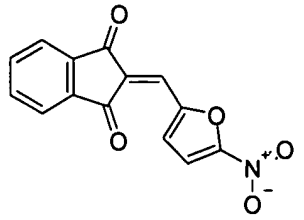
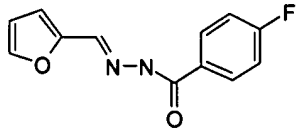
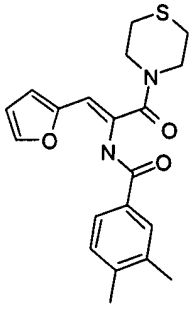
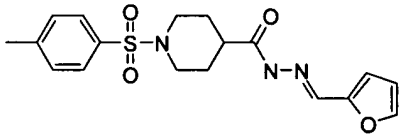
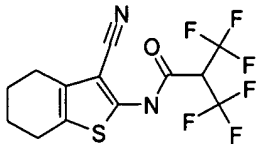
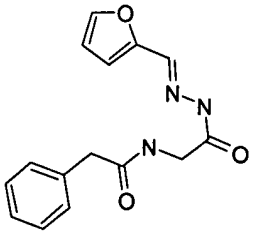
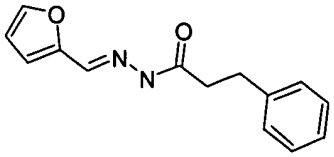
A3.262		50.1
A3.263		50.2
A3.264		50.3
A3.265		51.1
A3.266		51.3
A3.267		53.2*

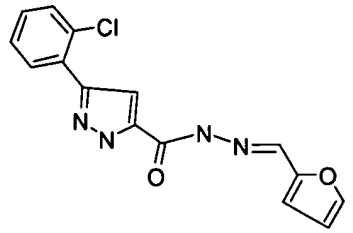
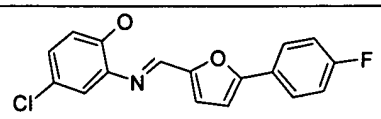
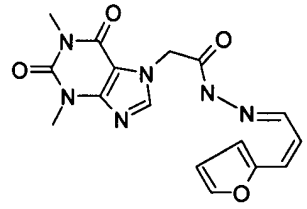
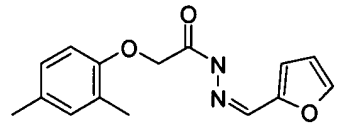
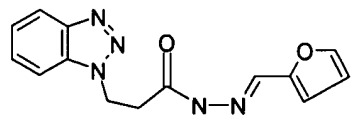
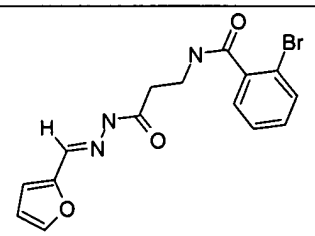
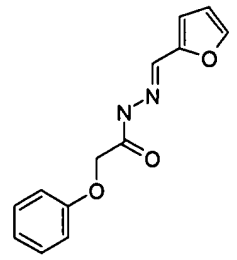
A3.268		52.1
A3.269		53.4
A3.270		54.0
A3.271		54.2
A3.272		54.4
A3.273		55.0*

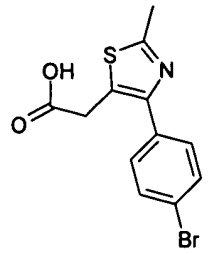
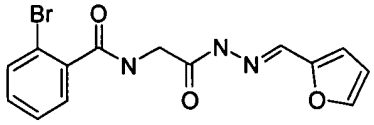
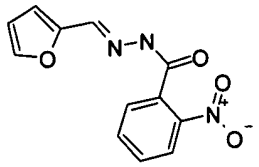
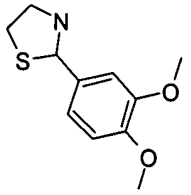
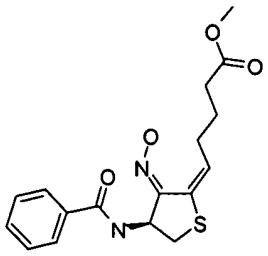
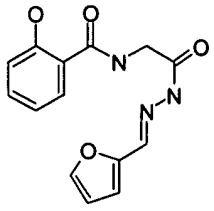
A3.274		55.6
A3.275		55.8
A3.276		56.4
A3.277		56.8
A3.278		58.3
A3.279		58.4
A3.280		60.0

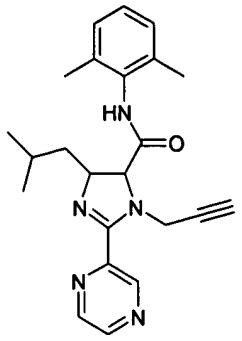
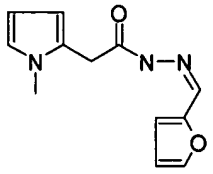
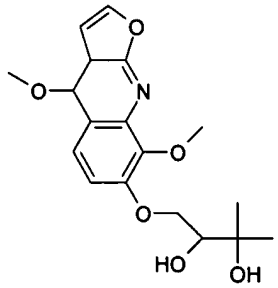
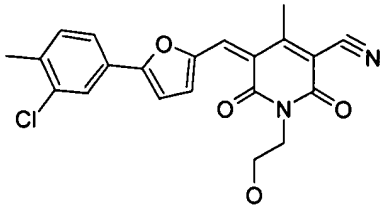
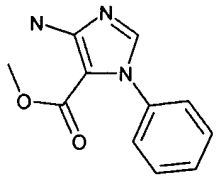
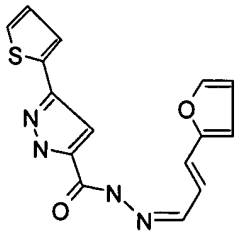
A3.281		62.4
A3.282		62.7
A3.283		62.7
A3.284		62.7
A3.285		63.1*
A3.286		64.2
A3.287		64.5
A3.288		64.9*

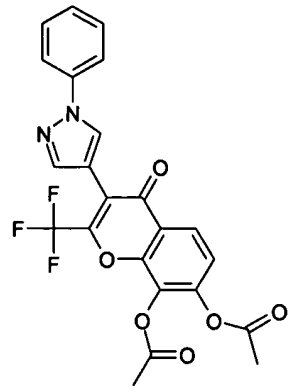
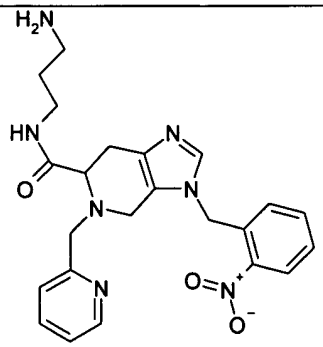
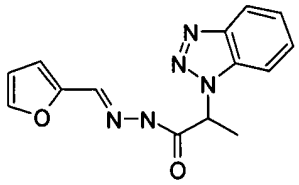
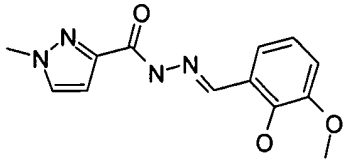
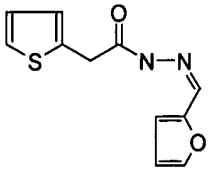
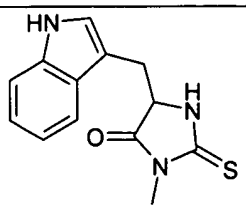
A3.289		65.1*
A3.290		65.8
A3.291		66.0*
A3.292		66.6
A3.293		67.1*
A3.294		68.0

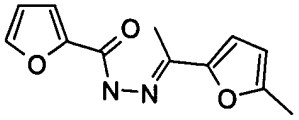
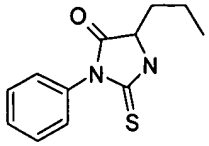
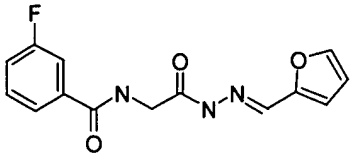
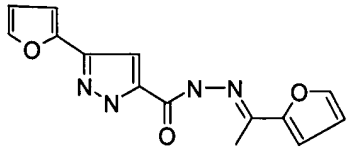
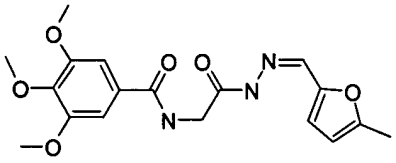
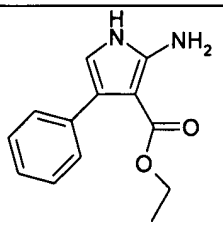
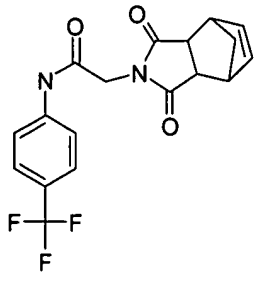
A3.295		68.0
A3.296		68.9
A3.297		68.9
A3.298		69.3
A3.299		71.4
A3.300		73.1*
A3.302		74.7

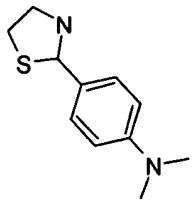
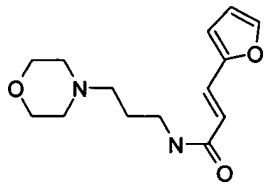
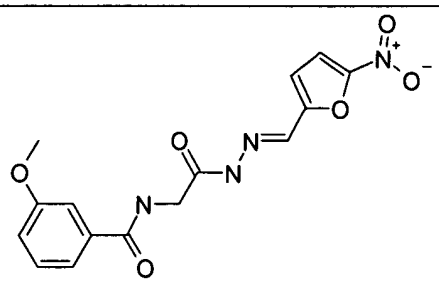
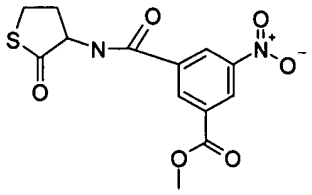
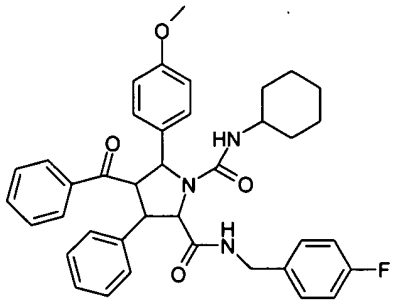
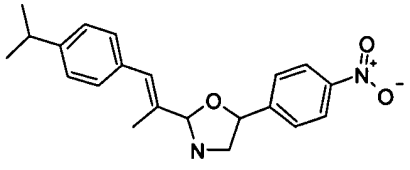
A3.303		75.8*
A3.305		77.3
A3.307		79.8*
A3.309		81.8*
A3.310		82.9
A3.311		85.8*
A3.312		87.5

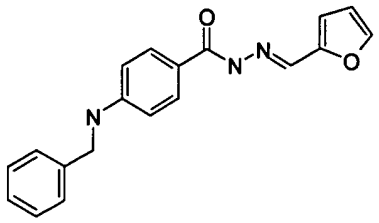
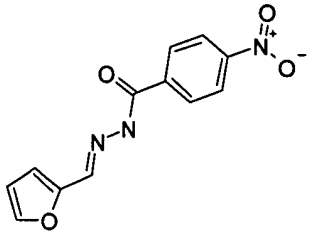
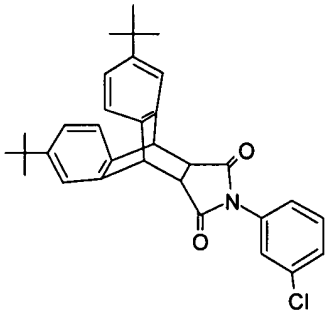
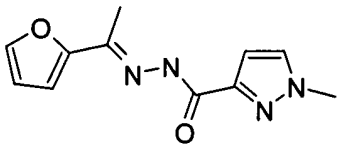
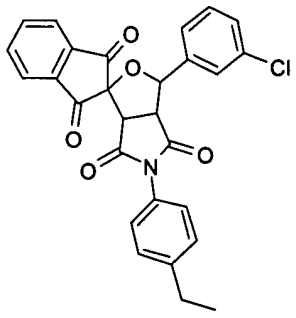
A3.313		88.3
A3.314		91.2*
A3.315		92.2
A3.316		92.1
A3.317		93.6
A3.318		98.8*

A3.319		102.6*
A3.320		112.8*
A3.321		117.3*
A3.322		125.4
A3.323		126.2*
A3.324		131.9*

A3.325		133.7*
A3.326		138.4
A3.327		146.5*
A3.328		142.2
A3.329		143.1
A3.330		146.5*

A3.331		152.4
A3.332		154.4*
A3.333		155.0*
A3.334		160.7*
A3.335		161.2*
A3.336		168.7*
A3.337		223.0*

A3.338		229.8*
A3.339		208.5*
A3.340		221.8*
A3.341		238.4*
A3.342		231.1*
A3.345		293.0*

A3.346		293.8*
A3.347		305.2*
A3.348		321.1*
A3.349		322.8*
A3.350		338.9*

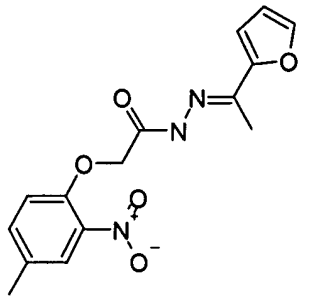
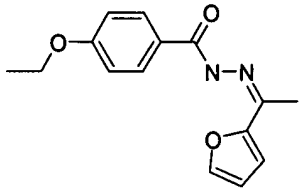
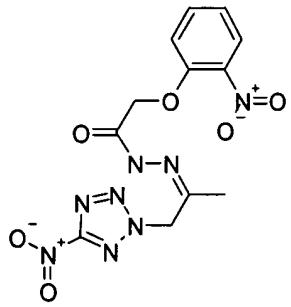
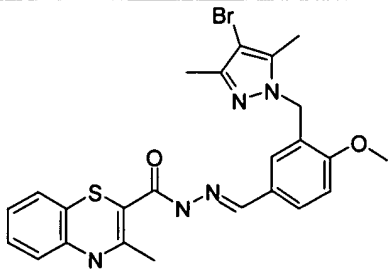
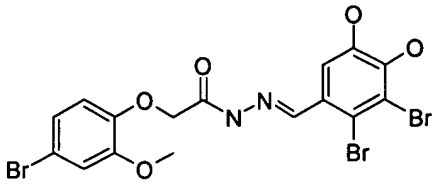
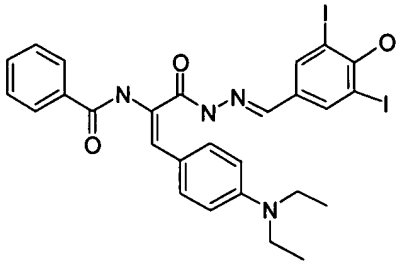
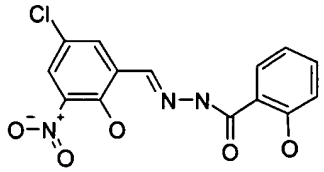
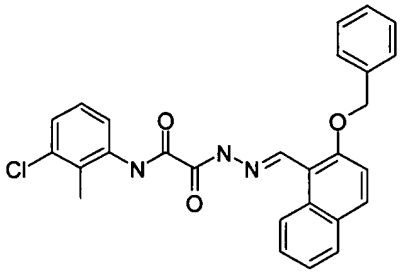
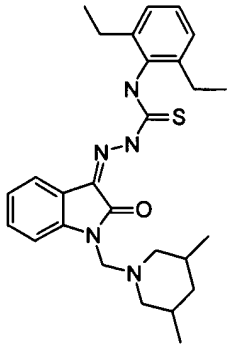
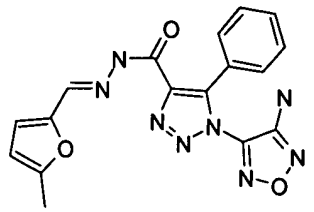
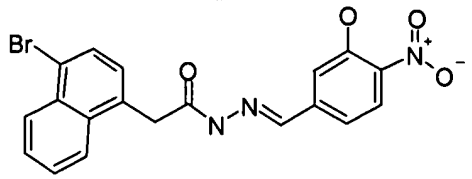
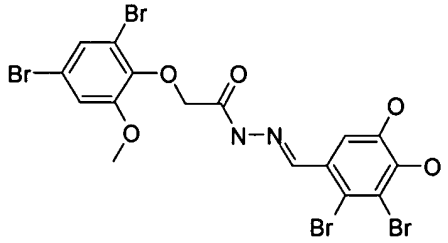
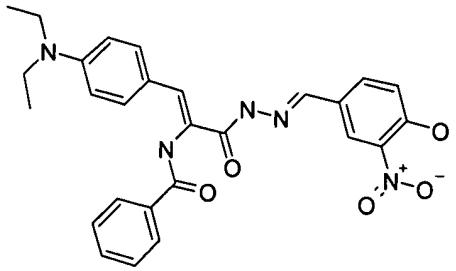
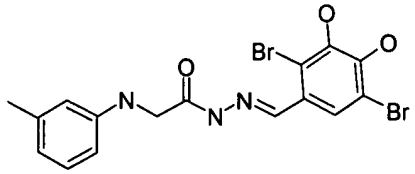
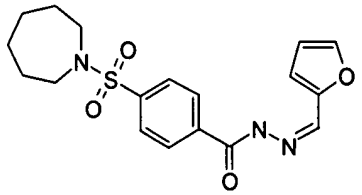
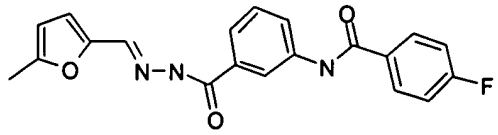
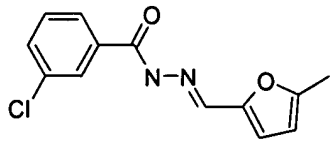
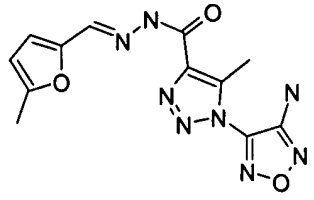
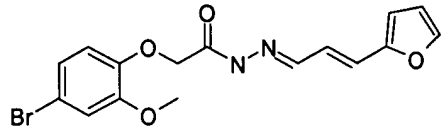
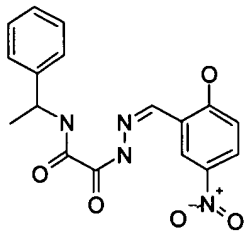
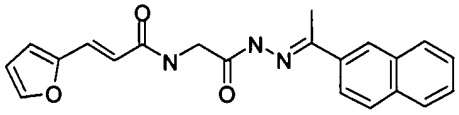
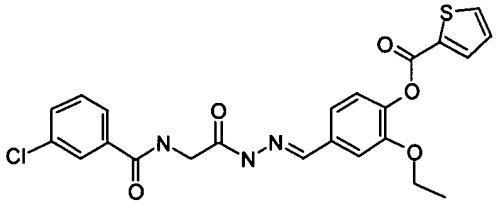
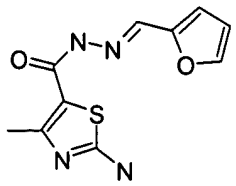
A3.351		422.4*
A3.352		451.4*

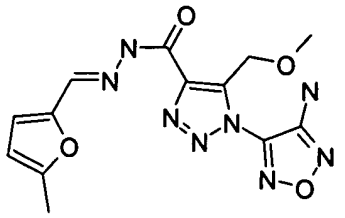
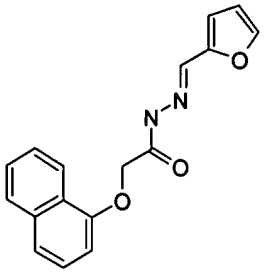
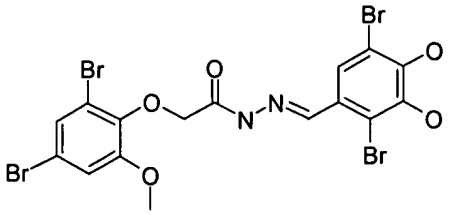
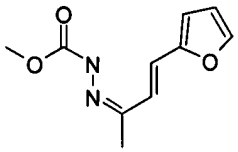
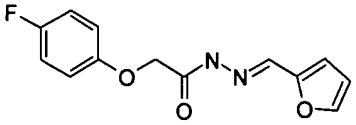
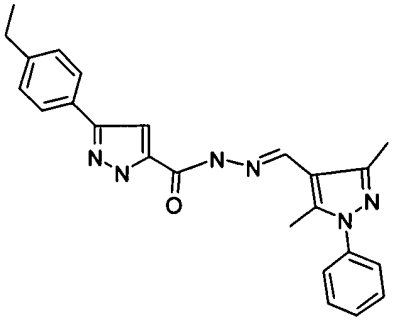
Table 4:

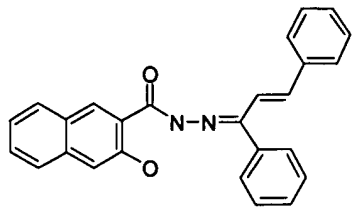
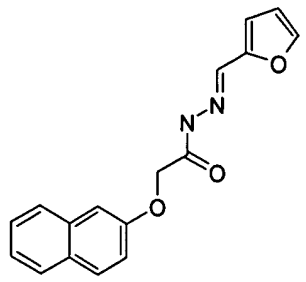
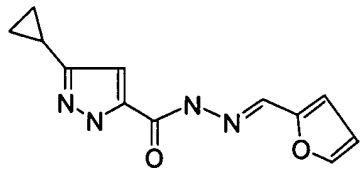
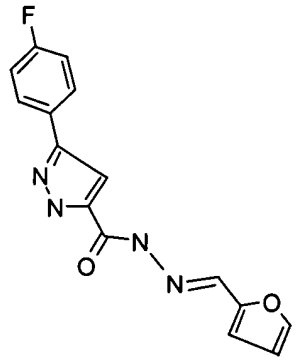
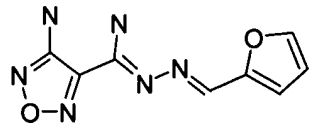
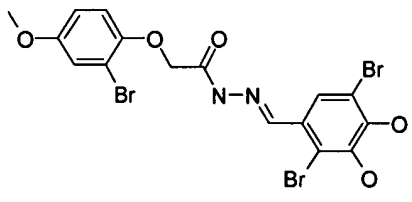
Compound ID.	Structure	$IC50_{APN}$ [µM]
A4.001		3.4
A4.002		4.8

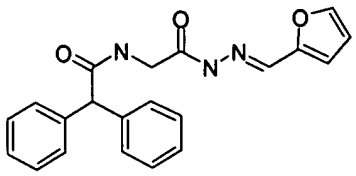
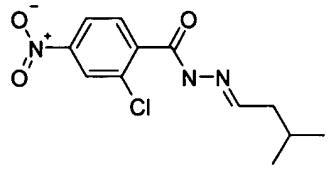
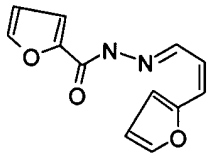
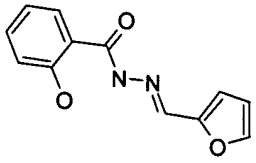
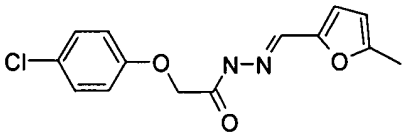
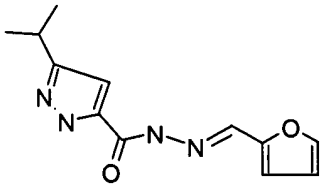
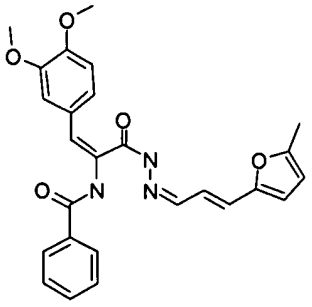
A4.003		5.0
A4.004		5.1
A4.005		5.8
A4.006		6.6
A4.007		6.7

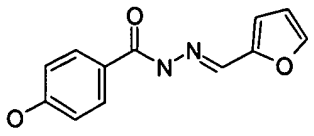
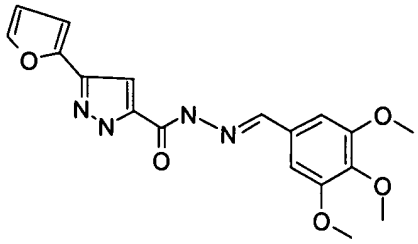
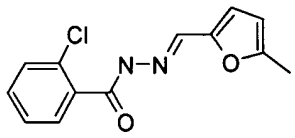
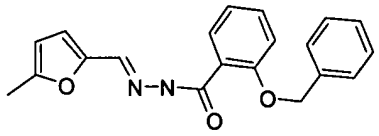
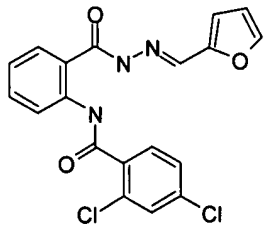
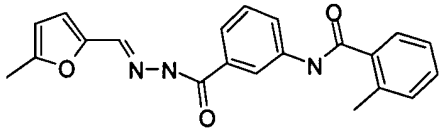
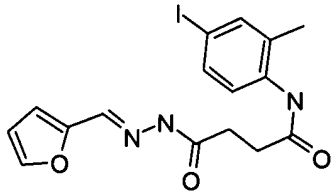
A4.008		6.9
A4.009		7.0
A4.010		7.2
A4.011		7.6
A4.012		7.8
A4.013		8.0
A4.014		9.8

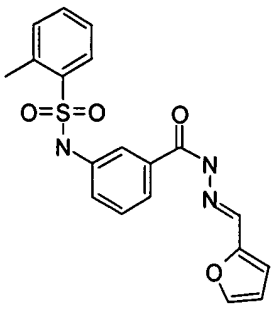
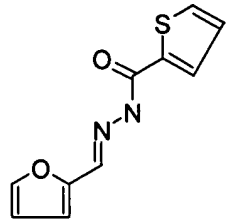
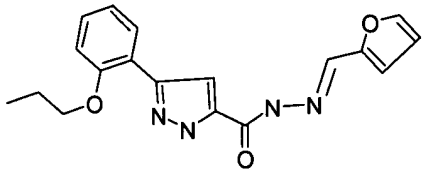
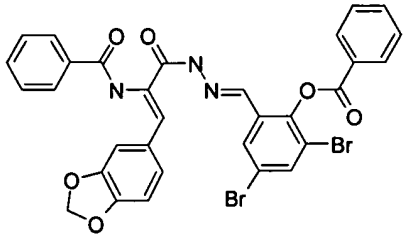
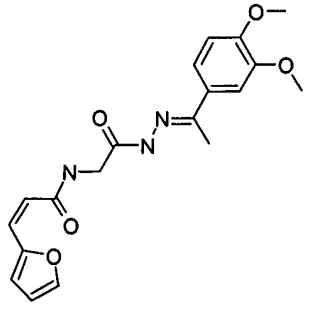
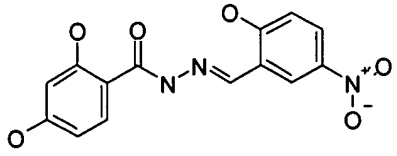
A4.015		10.5
A4.016		10.9
A4.017		11.0
A4.018		11.4
A4.019		12.0
A4.020		12.2
A4.021		12.3

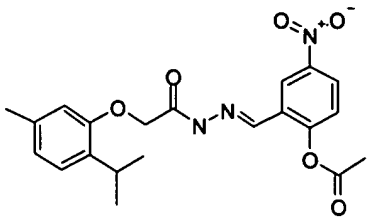
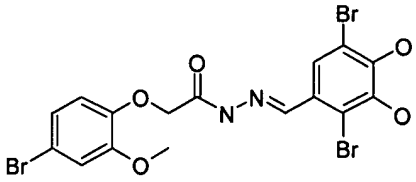
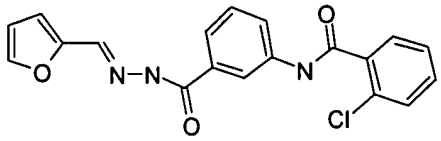
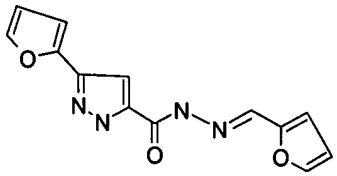
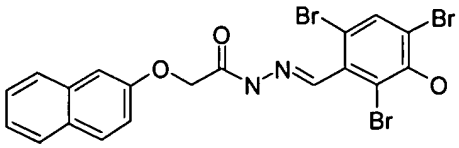
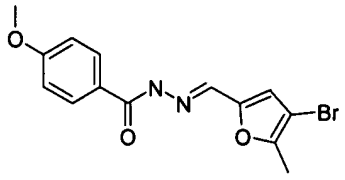
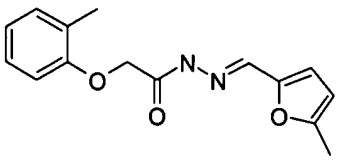
A4.022		12.5
A4.023		12.9
A4.024		13.2
A4.025		13.5
A4.026		13.6
A4.027		13.6

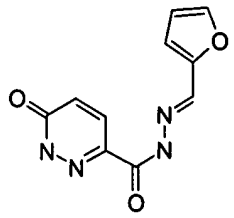
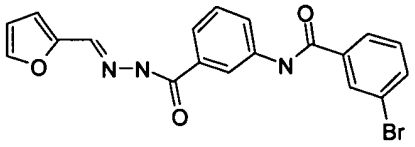
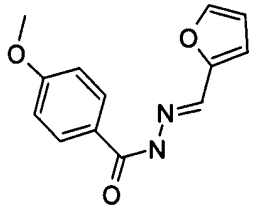
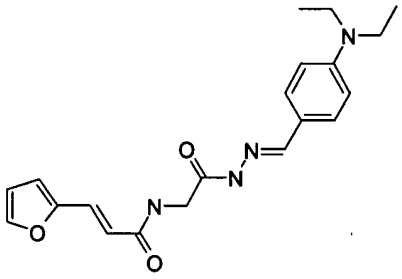
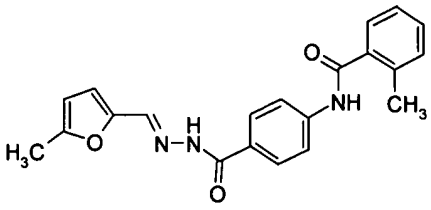
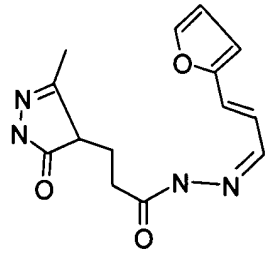
A4.028		13.7
A4.029		13.9
A4.030		14.3
A4.031		14.4
A4.032		14.6
A4.033		15.0

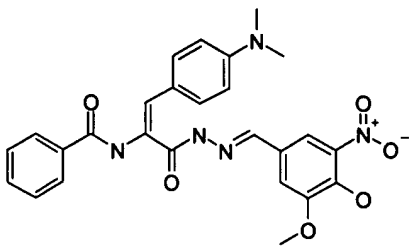
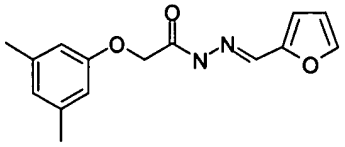
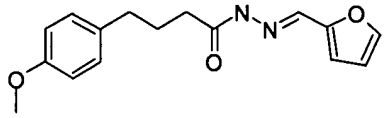
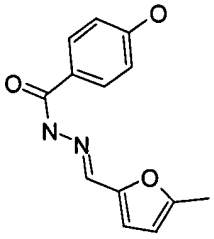
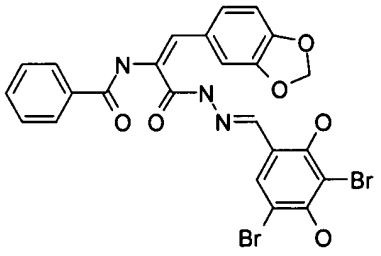
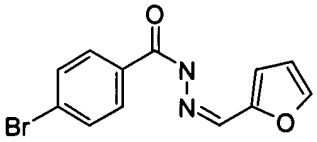
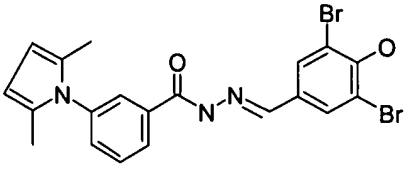
A4.034		15.6
A4.035		15.6
A4.036		16.0
A4.037		16.0
A4.038		16.0
A4.040		16.6
A4.041		16.7

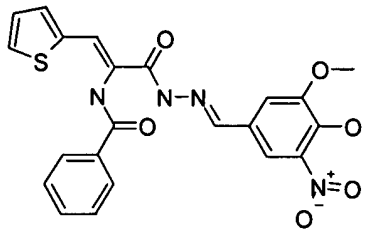
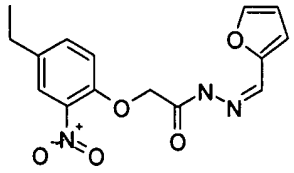
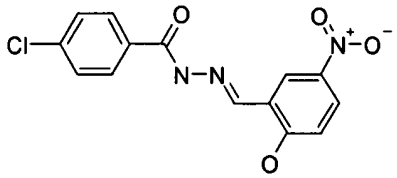
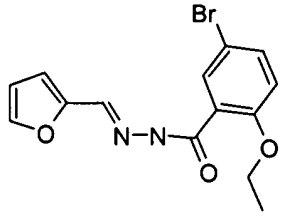
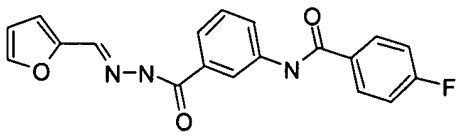
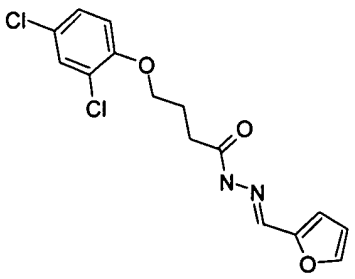
A4.042		16.8
A4.043		17.0
A4.044		17.7
A4.045		18.4
A4.046		18.7
A4.047		18.9
A4.048		9.5

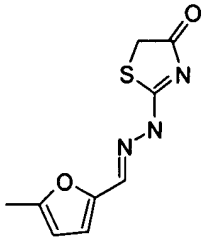
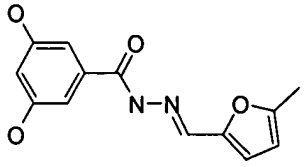
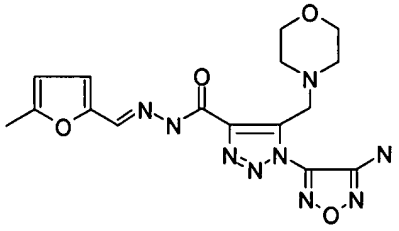
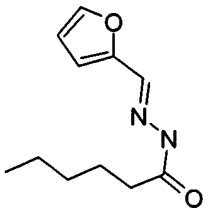
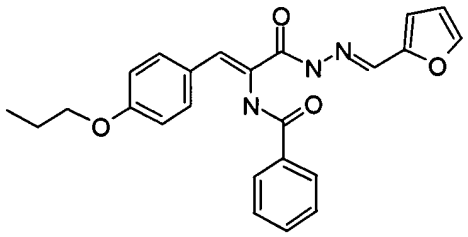
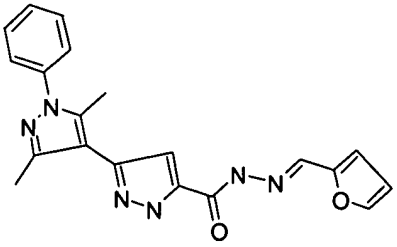
A4.049		19.2
A4.050		19.4
A4.051		19.5
A4.052		19.8
A4.053		19.9
A4.054		20.2

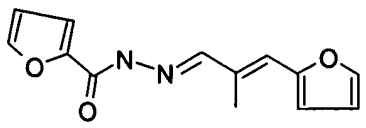
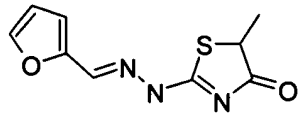
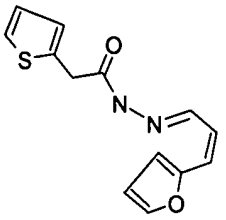
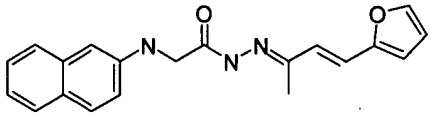
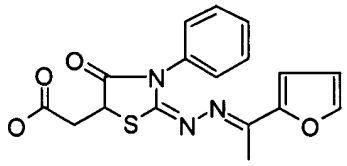
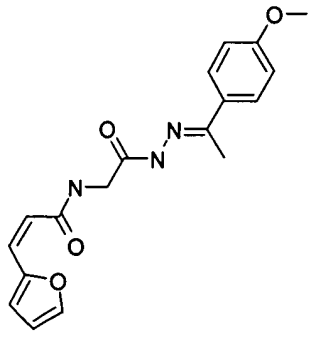
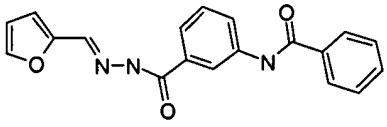
A4.055		20.3
A4.056		20.5
A4.057		20.6
A4.058		20.9
A4.059		21.0
A4.060		21.8
A4.061		22.2

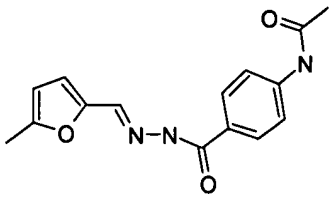
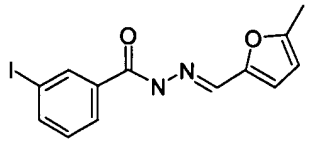
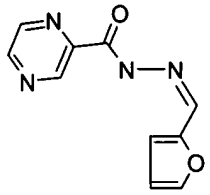
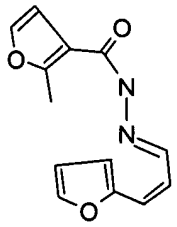
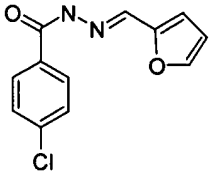
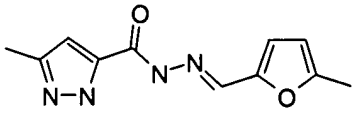
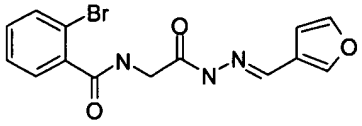
A4.063		22.4
A4.064		22.4
A4.065		22.6
A4.066		22.8
A4.067		22.8
A4.068		23.0

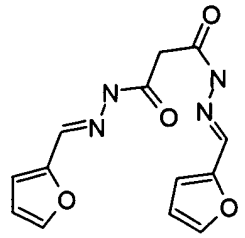
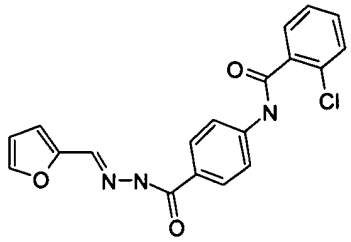
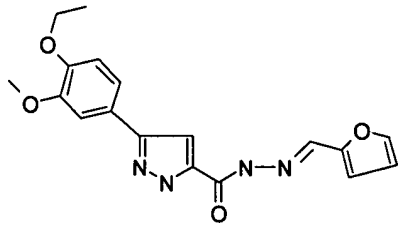
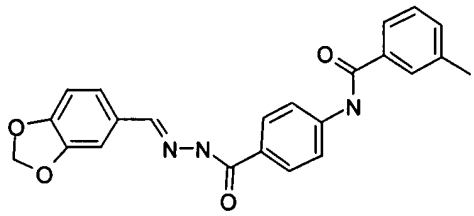
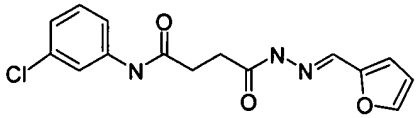
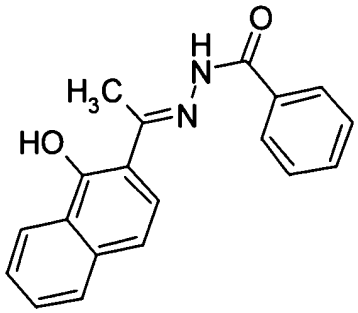
A4.069		23.0
A4.070		23.4
A4.071		23.4
A4.072		23.4
A4.073		23.6
A4.074		24.5
A4.075		24.9

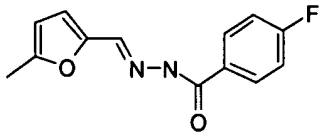
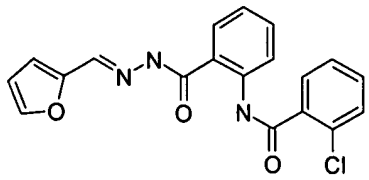
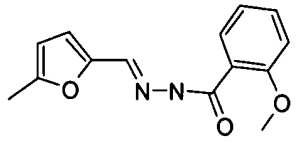
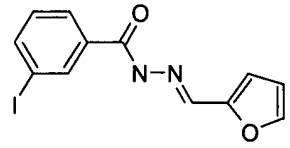
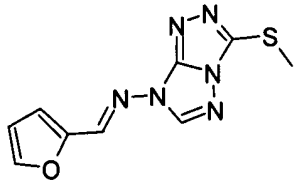
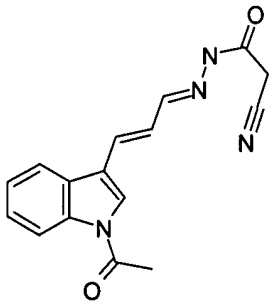
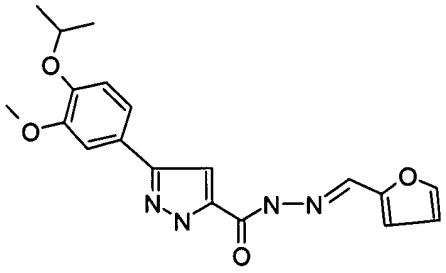
A4.076		25.1
A4.077		25.1
A4.078		25.7
A4.079		25.8
A4.080		25.9
A4.081		26.3

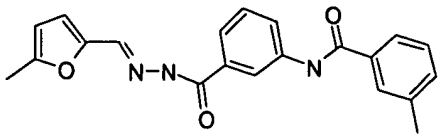
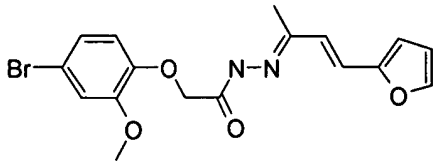
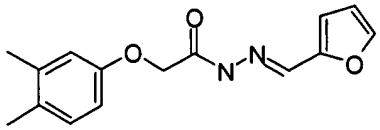
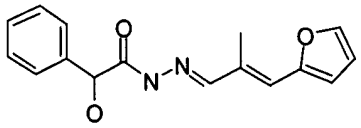
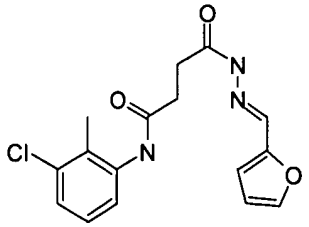
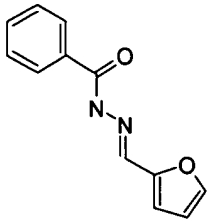
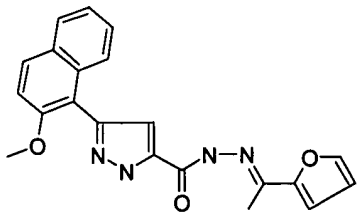
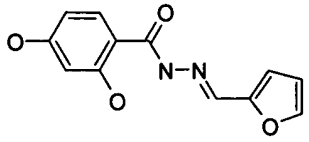
A4.082		26.4
A4.083		26.4
A4.084		26.7
A4.085		26.7
A4.086		27.3
A4.087		27.4

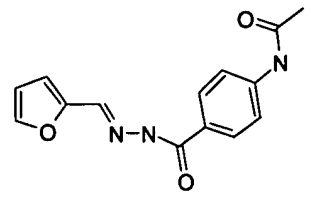
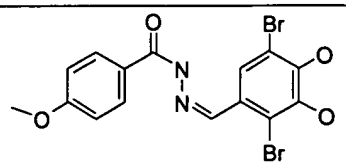
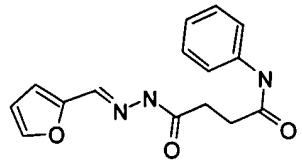
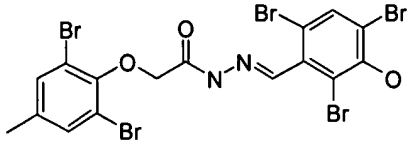
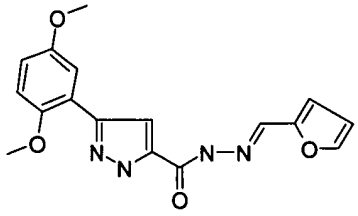
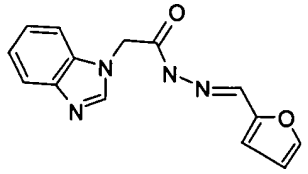
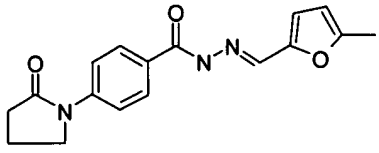
A4.088		27.5
A4.089		27.7
A4.090		28.0
A4.091		28.5
A4.092		28.6
A4.093		29.4
A4.094		29.5

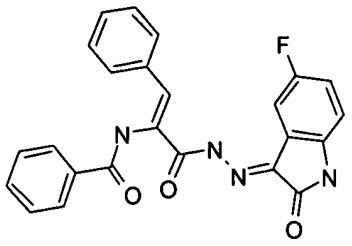
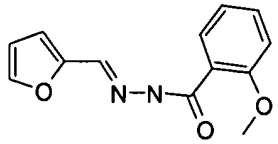
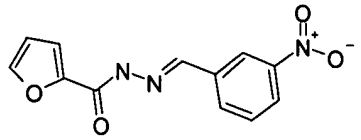
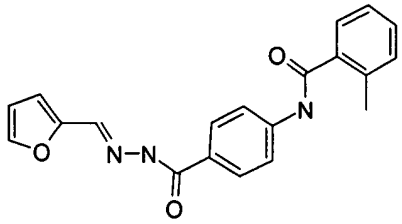
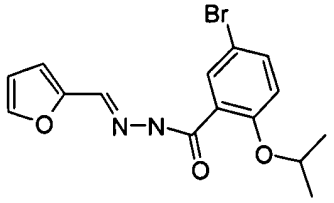
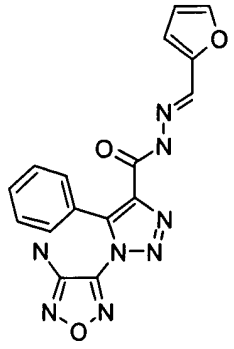
A4.095		29.7
A4.096		30.0
A4.097		30.1
A4.098		31.0
A4.099		30.8
A4.100		31.8
A4.101		31.9

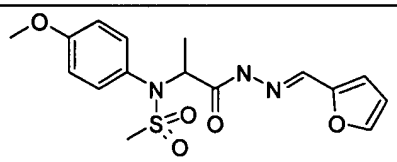
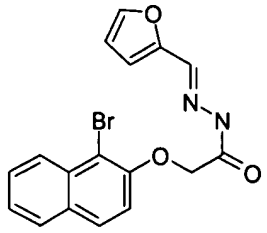
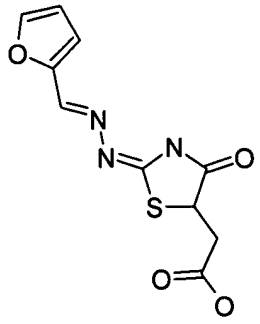
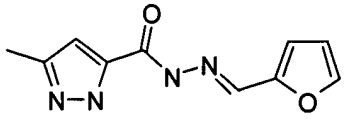
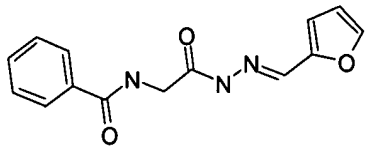
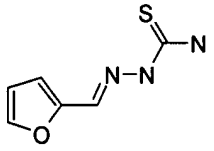
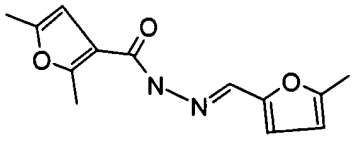
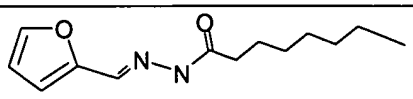
A4.102		32.4
A4.103		32.5
A4.104		33.4
A4.105		33.8*
A4.106		34.0
A4.107		34.2

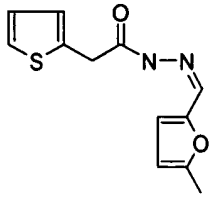
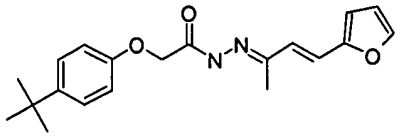
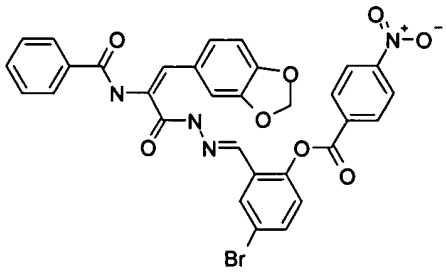
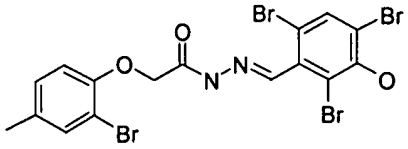
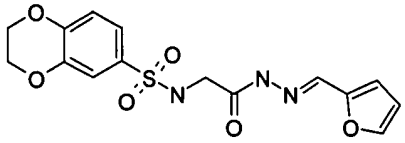
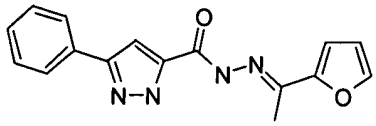
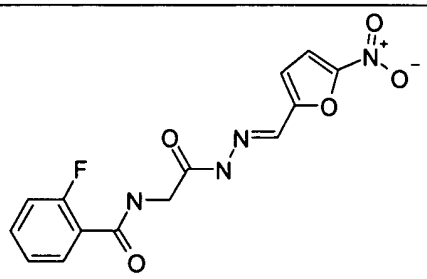
A4.108		34.4
A4.109		34.7
A4.110		34.7
A4.111		34.7
A4.112		34.7
A4.113		35.5
A4.114		36.1

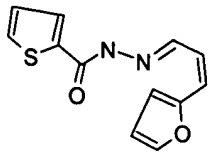
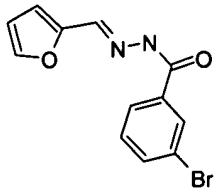
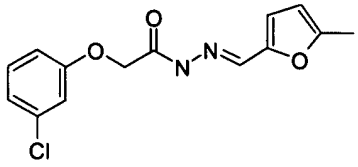
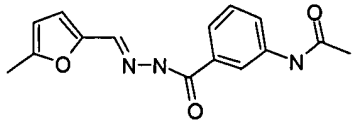
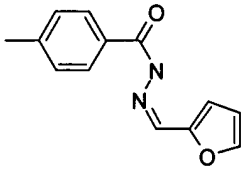
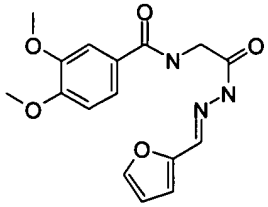
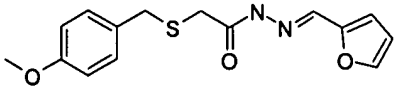
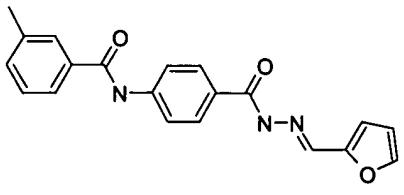
A4.115		36.2
A4.116		36.3
A4.117		36.3
A4.118		36.3
A4.119		36.6
A4.120		37.7
A4.121		38.2
A4.122		38.3

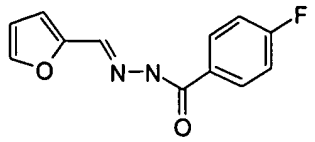
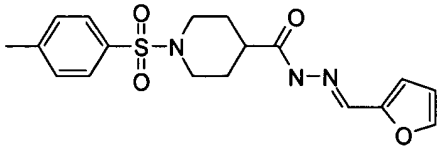
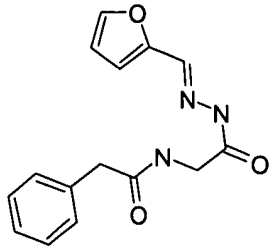
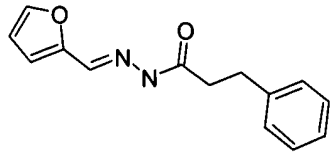
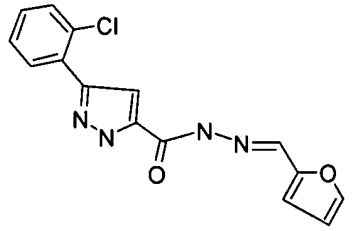
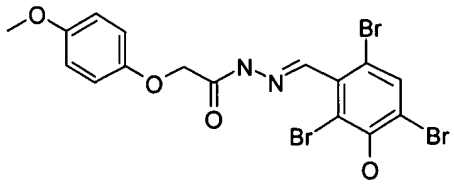
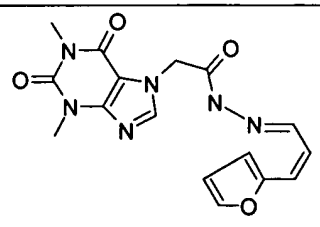
A4.123		38.4
A4.124		39.7*
A4.125		41.1
A4.126		42.2
A4.127		43.2
A4.128		43.3
A4.129		44.2

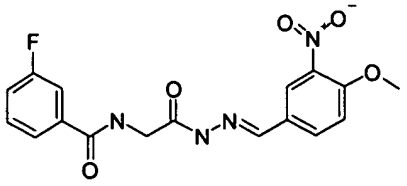
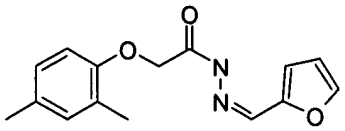
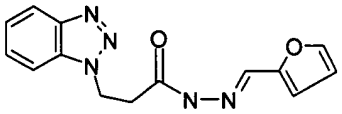
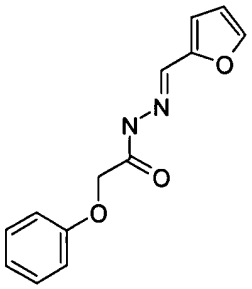
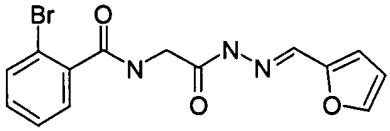
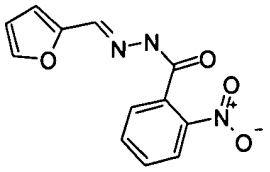
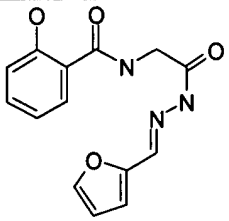
A4.130		44.2
A4.131		44.7
A4.132		45.4
A4.133		45.4
A4.134		46.6
A4.135		46.6

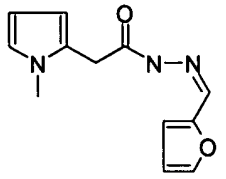
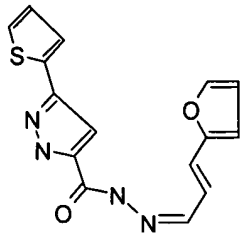
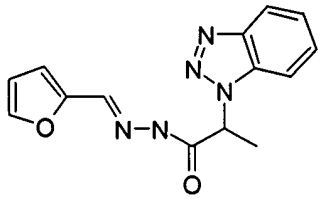
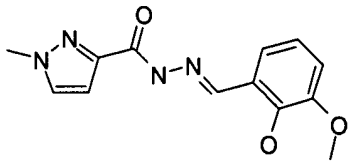
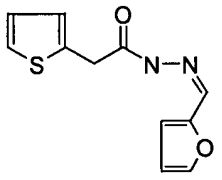
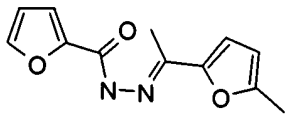
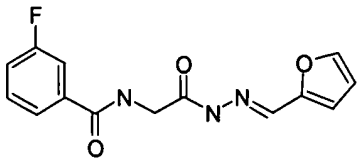
A4.136		47.0
A4.137		47.3
A4.138		48.1*
A4.139		48.2
A4.140		49.4*
A4.141		50.0
A4.142		50.2
A4.143		50.3

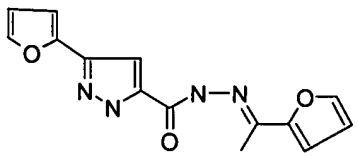
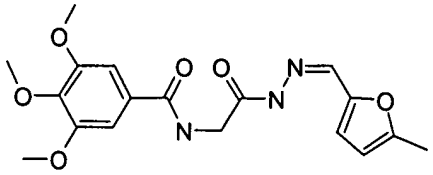
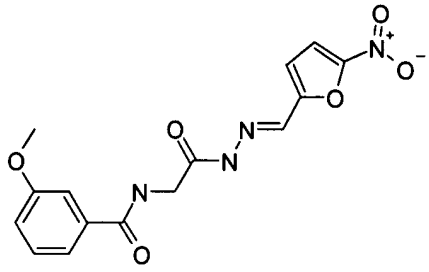
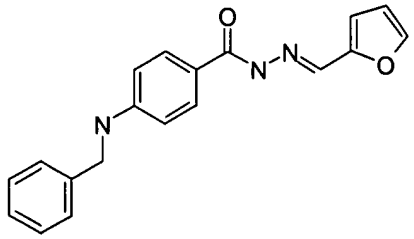
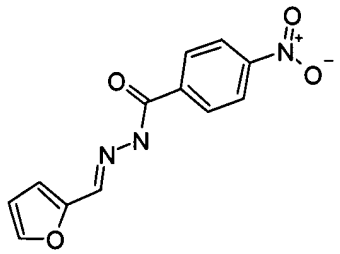
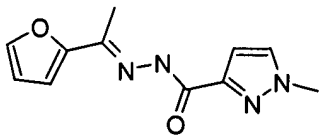
A4.144		51.1
A4.145		53.4
A4.146		54.2
A4.147		54.2*
A4.148		55.6
A4.149		58.3
A4.150		60.0

A4.151		62.7
A4.152		62.7
A4.153		62.7
A4.154		63.1*
A4.155		64.2
A4.156		64.9*
A4.157		66.0*
A4.158		67.1*

A4.159		68.9
A4.160		69.3
A4.161		73.1*
A4.162		74.7
A4.163		75.8*
A4.164		76.4*
A4.166		79.8*

A4.167		80.4*
A4.168		81.8*
A4.169		82.9
A4.170		87.5
A4.171		91.2*
A4.172		91.2
A4.173		98.8*

A4.174		112.8*
A4.175		131.9*
A4.176		146.5*
A4.177		142.2
A4.178		143.1
A4.179		152.4
A4.180		155.0*

A4.181		160.7*
A4.182		161.2*
A4.183		221.8*
A4.184		293.8*
A4.185		305.2*
A4.186		322.8*

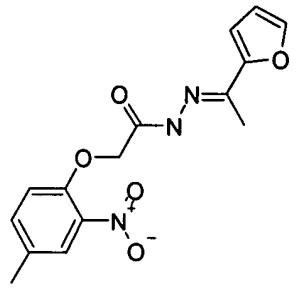
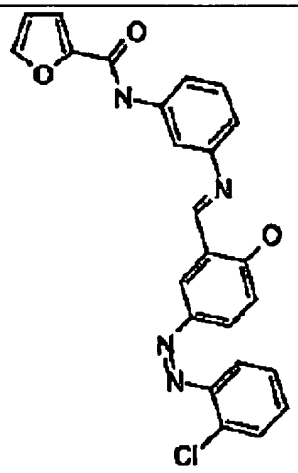
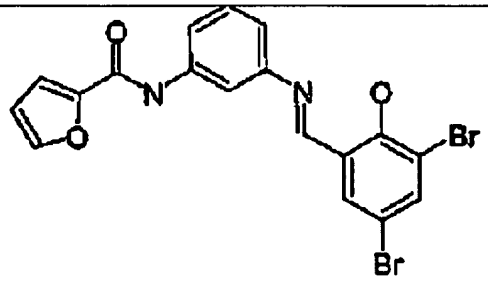
A4.187		422.4*

Table 5:

Compound ID.	Structure	$IC50_{APN}$ [µM]
A5.001		3.6
A5.003		8.2

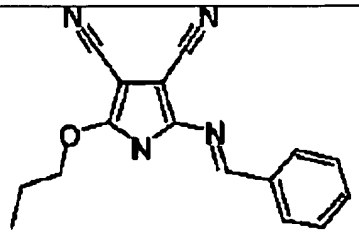
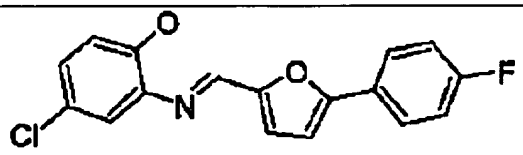
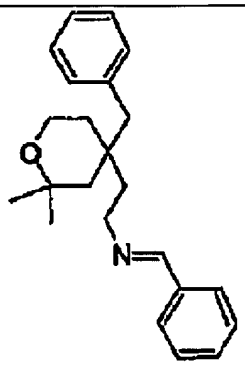
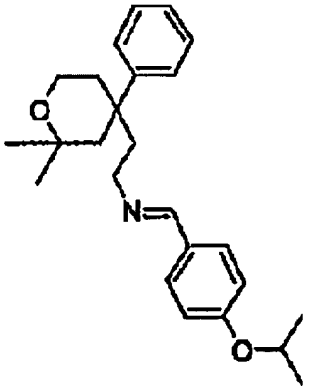
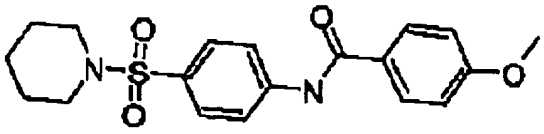
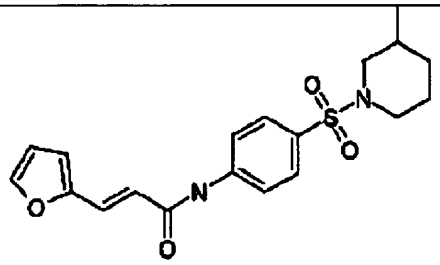
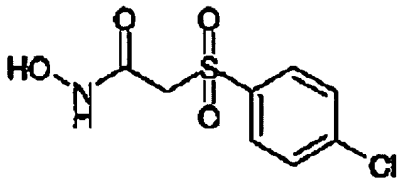
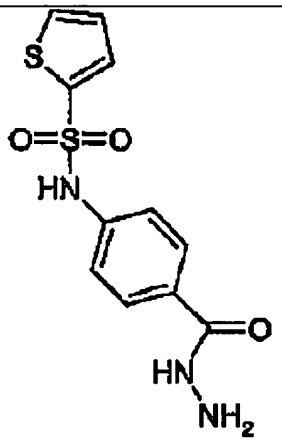
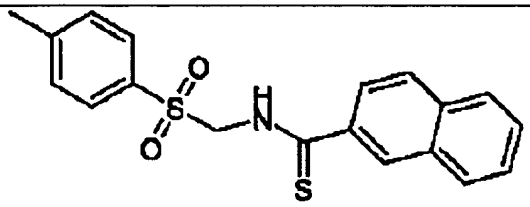
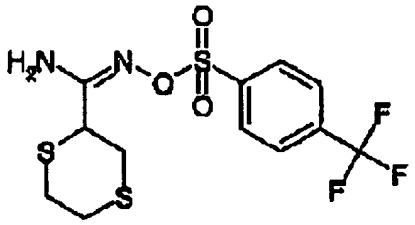
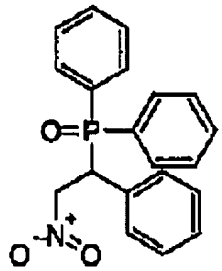
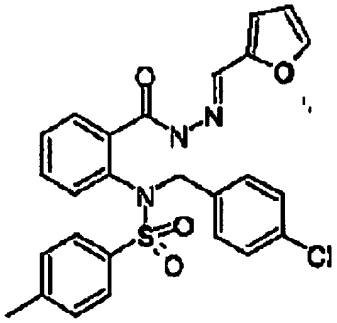
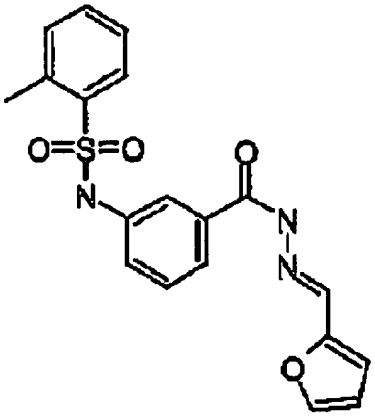
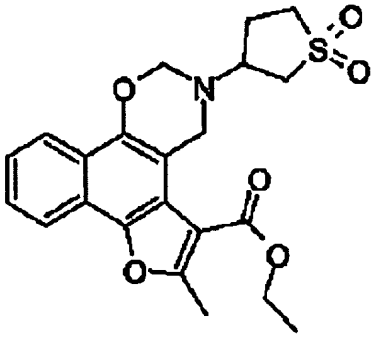
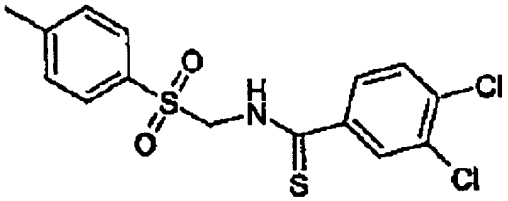
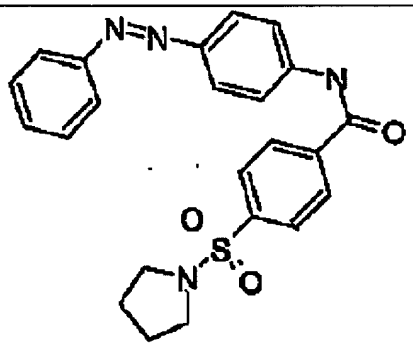
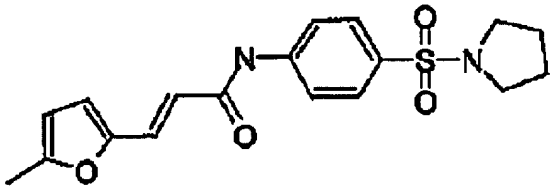
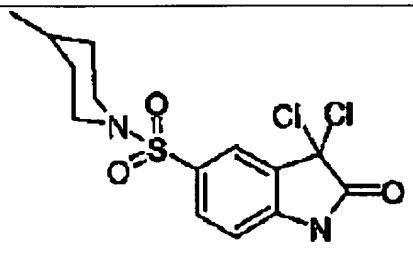
A5.004		20.0
A5.005		77.3
A5.006		93.6
A5.007		197.4*

Table 6:

Compound ID.	Structure	$IC50_{APN}$ [µM]
A6.001		8.4
A6.002		8.4
A6.003		11.5
A6.004		11.8
A6.005		11.8

A6.006		13.4
A6.007		16.3
A6.008		16.4
A6.009		19.2

A6.010		22.3
A6.011		18.0
A6.012		21.6
A6.013		24.8
A6.015		37.2

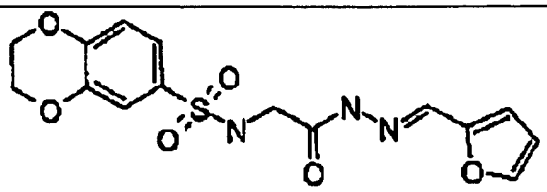
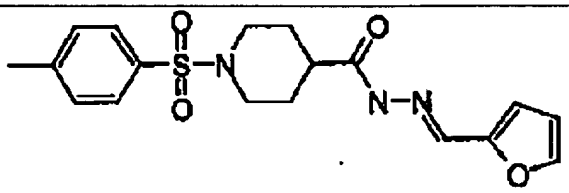
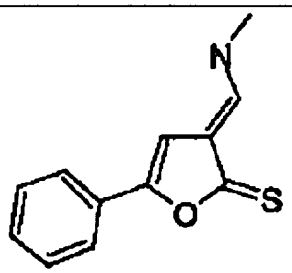
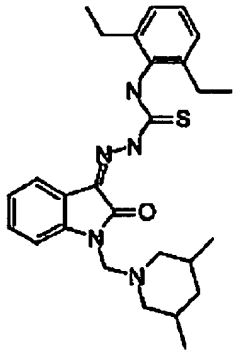
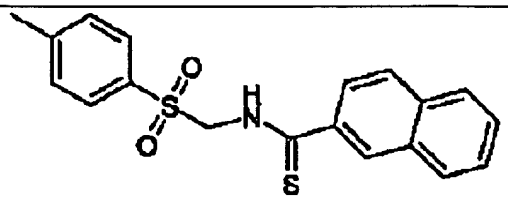
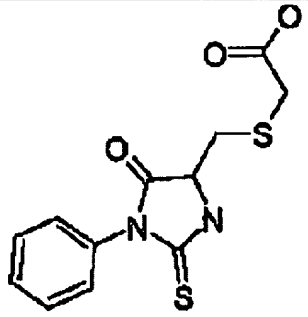
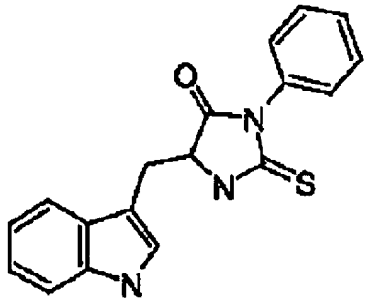
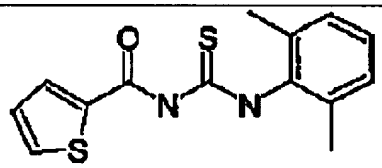
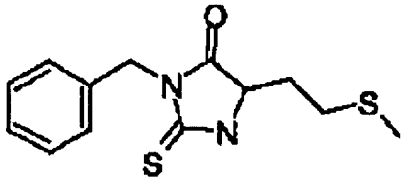
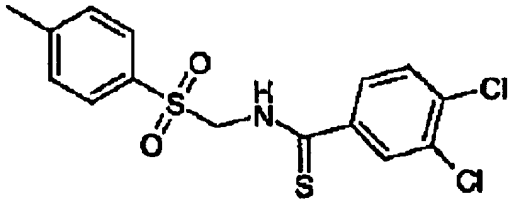
A6.016		55.6
A6.017		69.3

Table 7:

Compound ID.	Structure	IC50APN [µM]
A7.001		6.0
A7.002		6.7

A7.004		11.8
A7.005		12.0
A7.006		12.4
A7.007		12.9
A7.008		14.1
A7.010		18.0

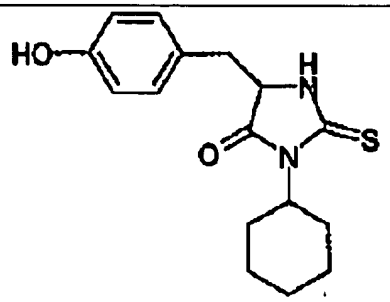
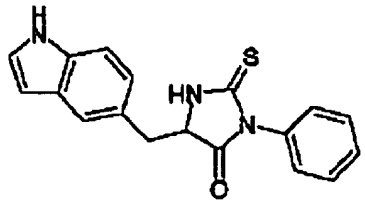
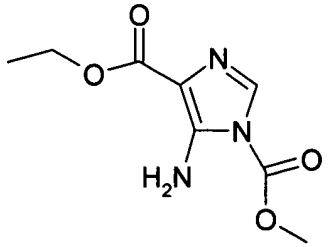
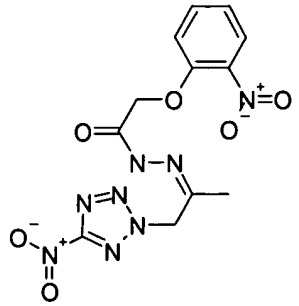
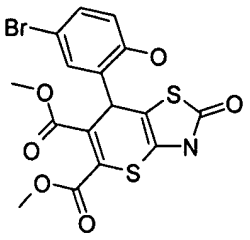
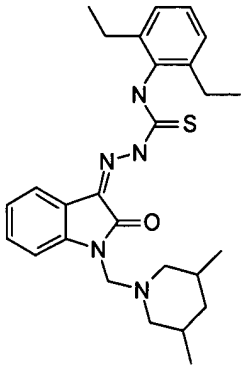
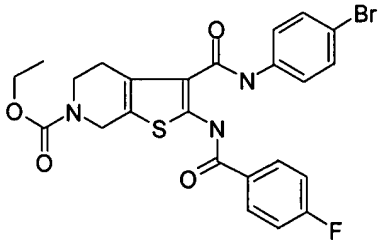
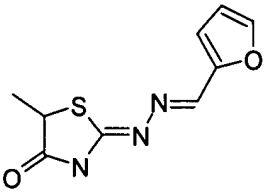
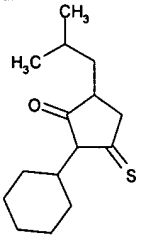
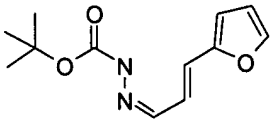
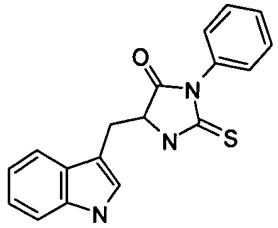
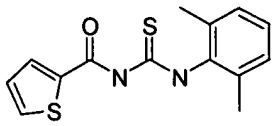
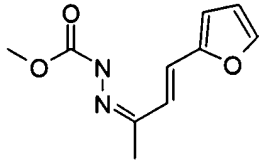
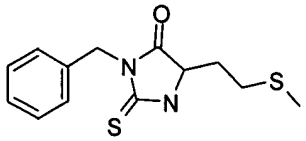
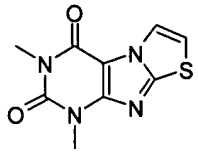
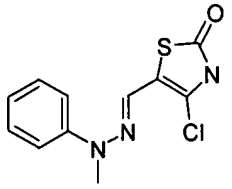
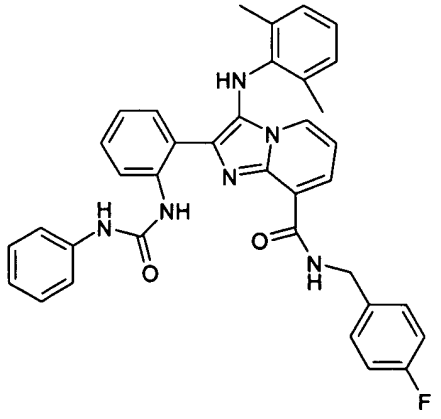
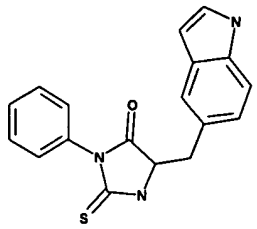
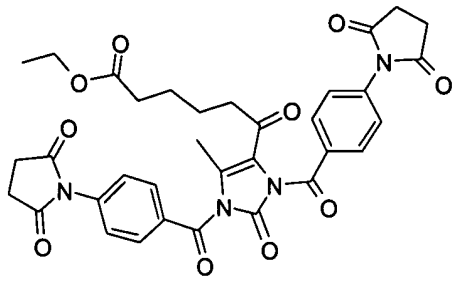
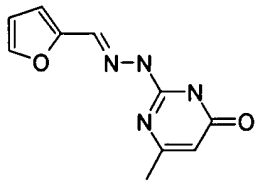
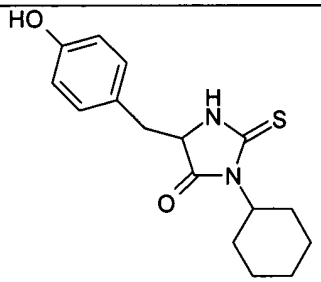
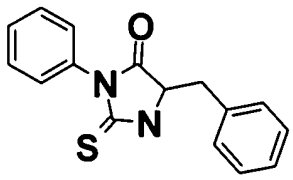
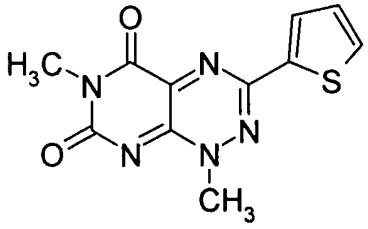
A7.011		21.3
A7.012		36.9

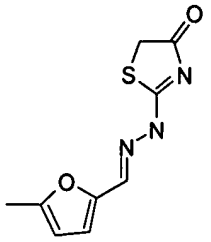
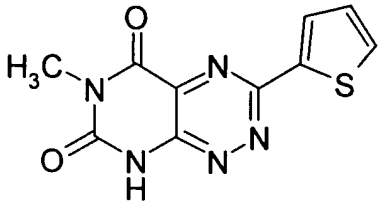
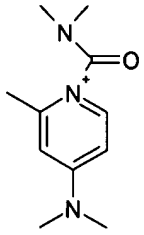
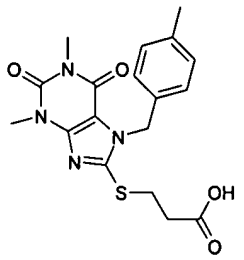
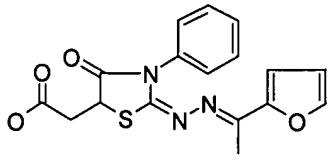
Table 8:

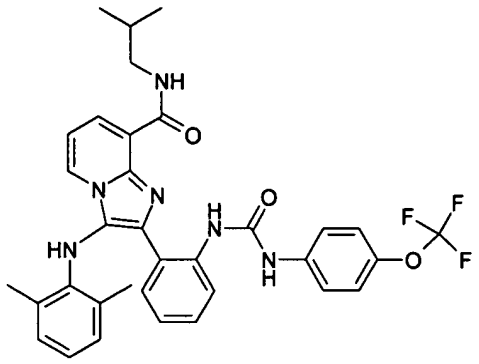
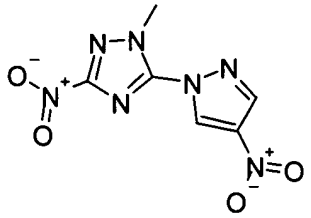
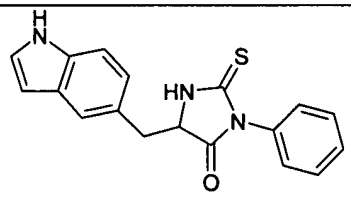
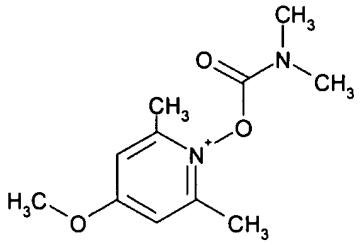
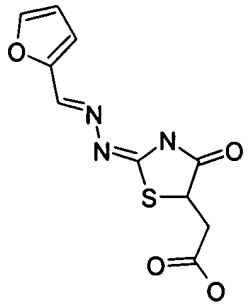
Compound ID.	Structure	$IC50_{APN}$ [µM]
A8.001		0.9*
A8.002		3.4

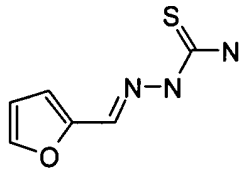
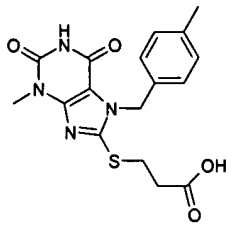
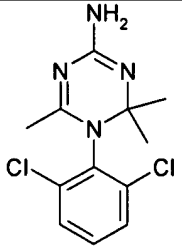
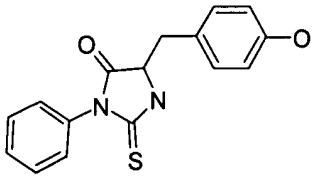
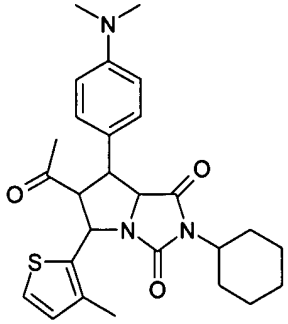
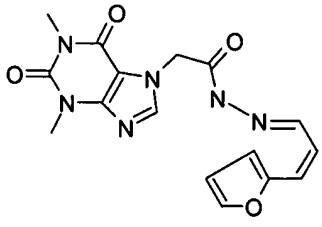
A8.003		4.7
A8.004		6.7
A8.005		7.3
A8.006		8.0
A8.007		8.0
A8.008		10.8

A8.009		12.4
A8.010		12.9
A8.011		13.5
A8.012		14.1
A8.013		14.3
A8.014		14.4
A8.015		14.9

A8.016		14.9
A8.017		15.6
A8.018		18.2
A8.019		21.3
A8.020		26.1
A8.021		25.0

A8.022		26.4
A8.023		22.6
A8.024		27.6
A8.025		28.0
A8.026		28.6

A8.027		31.4
A8.028		34.4
A8.029		36.9
A8.030		42.4
A8.031		48.1*

A8.032		50.0
A8.033		53.2*
A8.034		59.8
A8.035		66.6
A8.036		68.0
A8.037		79.8*

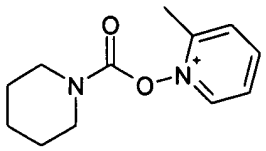
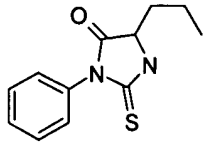
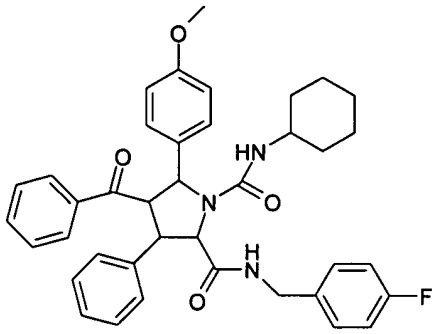
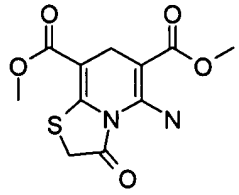
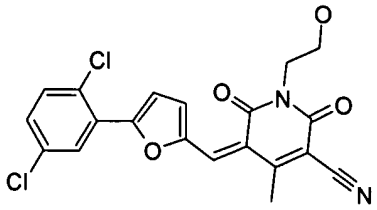
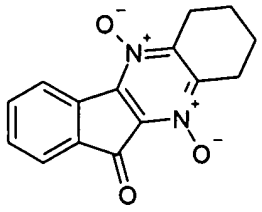
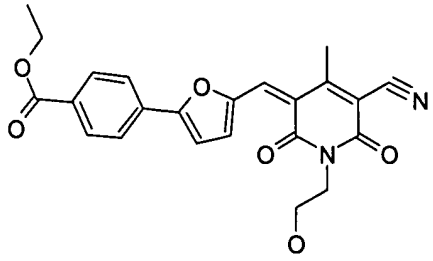
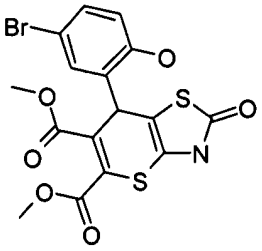
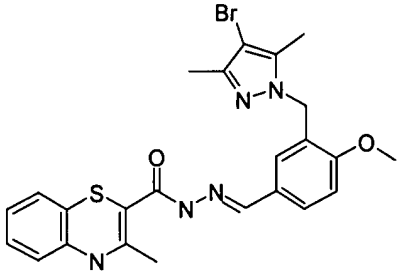
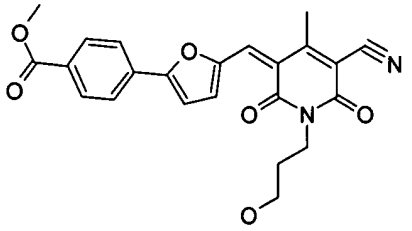
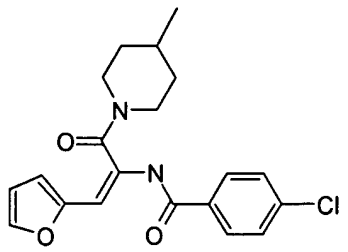
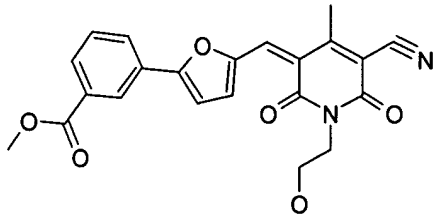
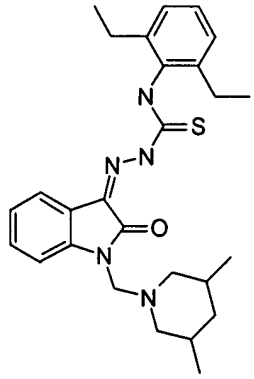
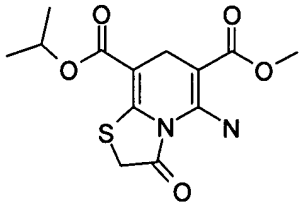
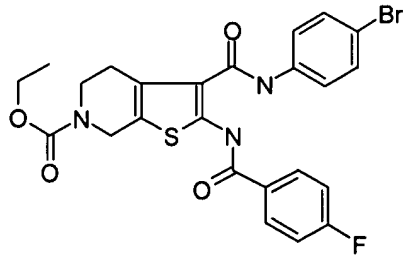
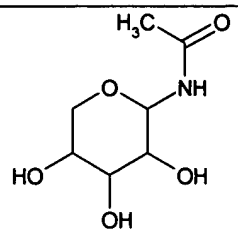
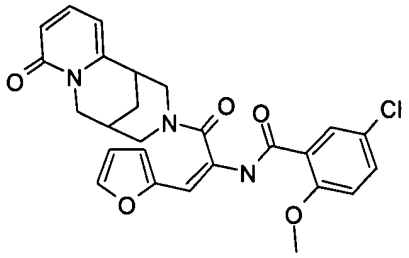
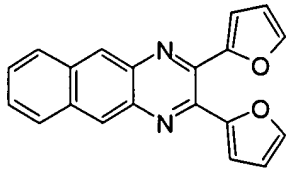
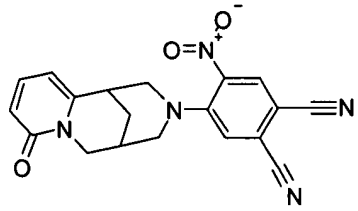
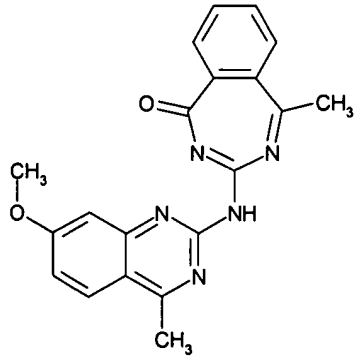
A8.038		96.7*
A8.040		154.4*
A8.041		231.1*

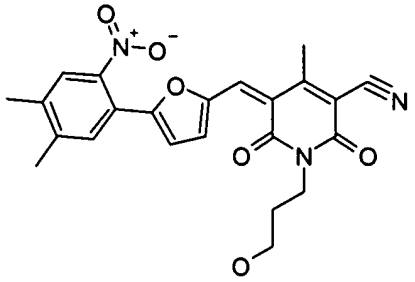
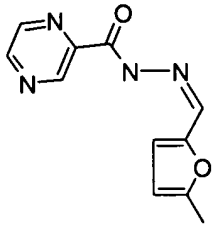
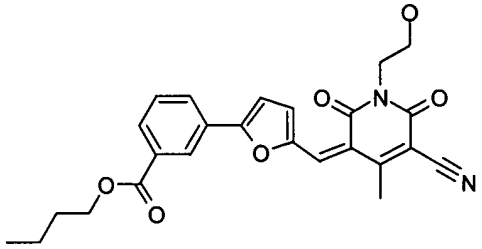
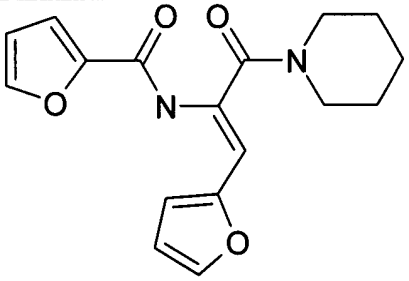
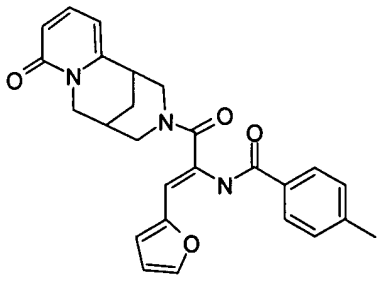
Table 9:

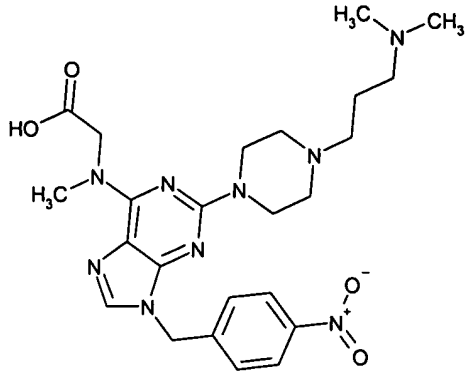
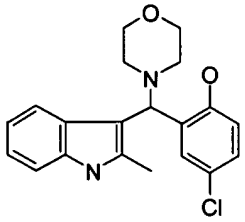
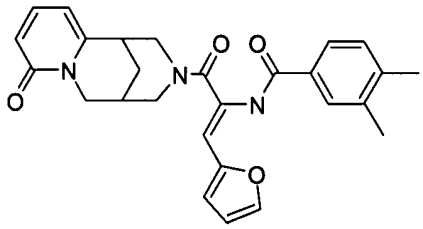
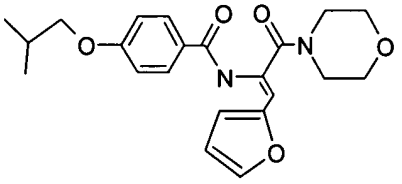
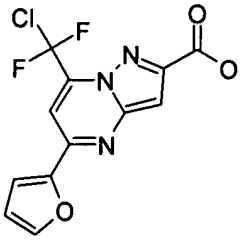
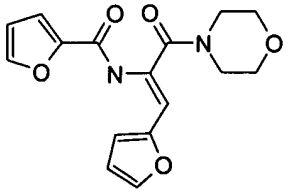
	Structure	$IC50_{APN}$ [µM]
A9.001		'very high active', beyond measure
A9.002		1.2*

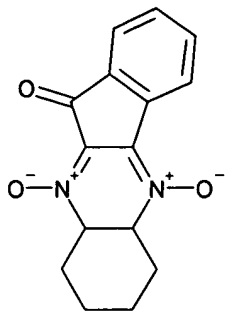
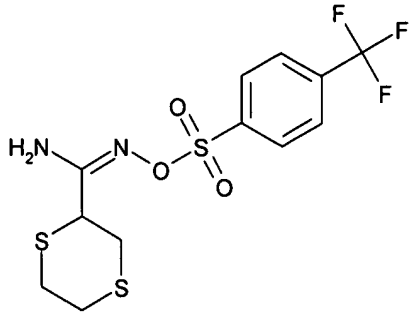
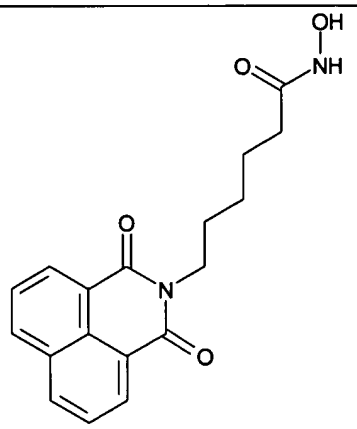
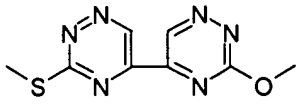
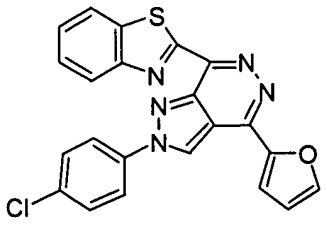
A9.003		2.0*
A9.005		2.7*
A9.006		4.7
A9.007		4.8
A9.008		5.0

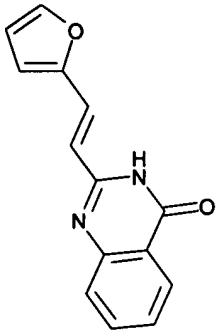
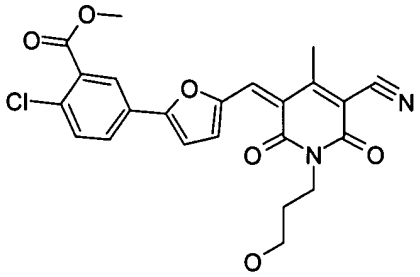
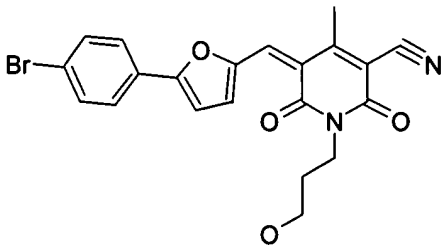
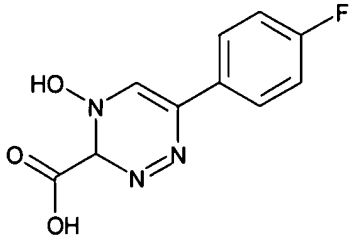
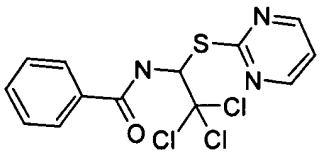
A9.009		6.2
A9.010		6.3
A9.011		6.7
A9.012		5.9
A9.013		7.3

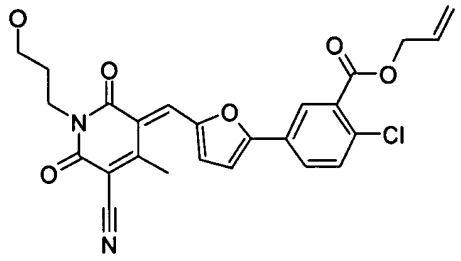
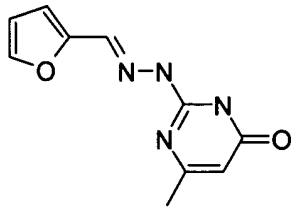
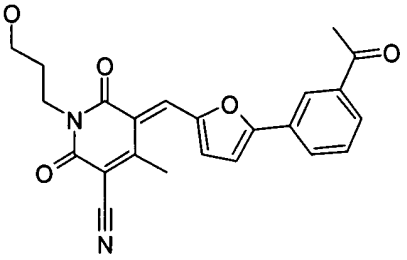
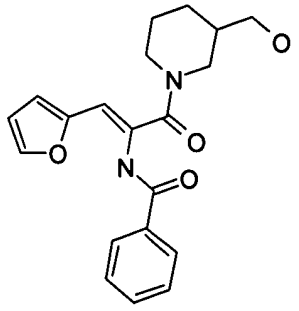
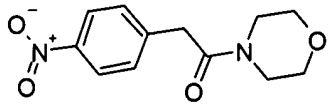
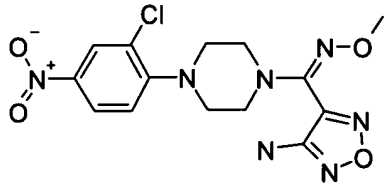
A9.014		7.3
A9.015		8.1
A9.016		8.9
A9.017		8.9
A9.018		8.9

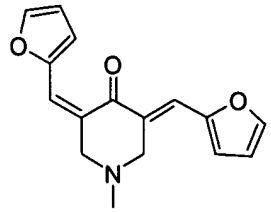
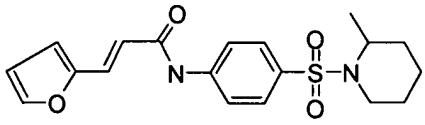
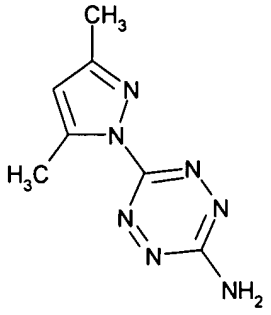
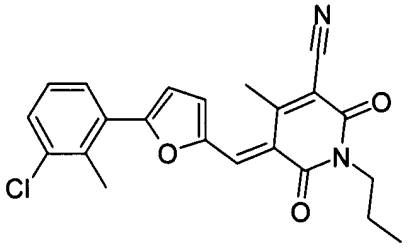
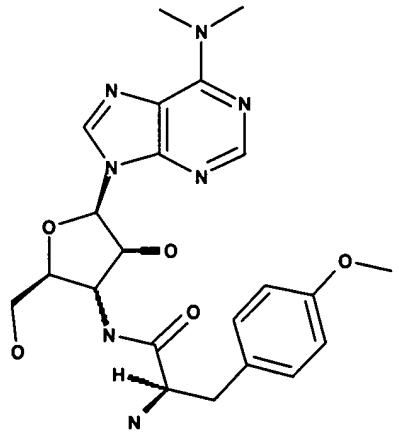
A9.019		9.7
A9.020		9.8
A9.021		10.2*
A9.022		10.6
A9.023		11.0

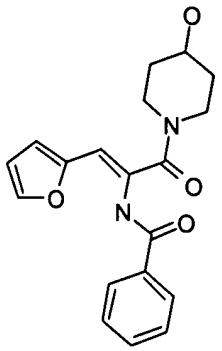
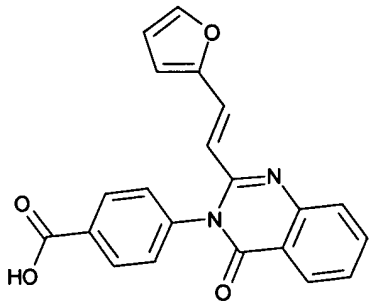
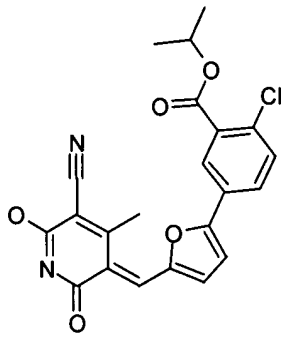
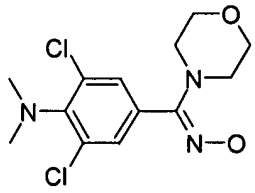
A9.024		11.8
A9.025		11.7
A9.026		11.8
A9.027		13.1
A9.028		13.2
A9.029		13.5

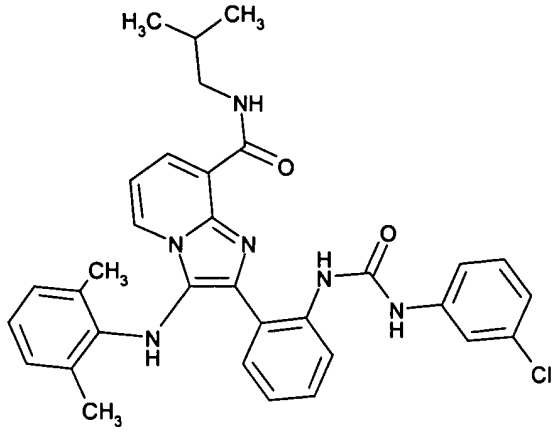
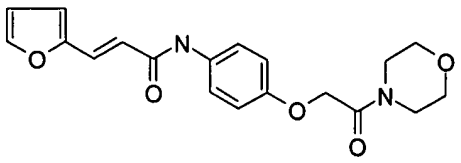
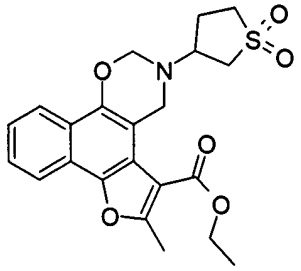
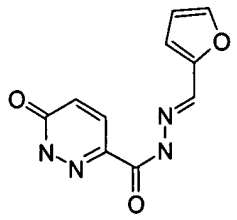
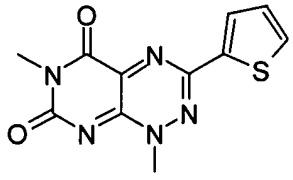
A9.030		13.7
A9.031		13.4
A9.032		14.1
A9.033		14.3
A9.034		14.3

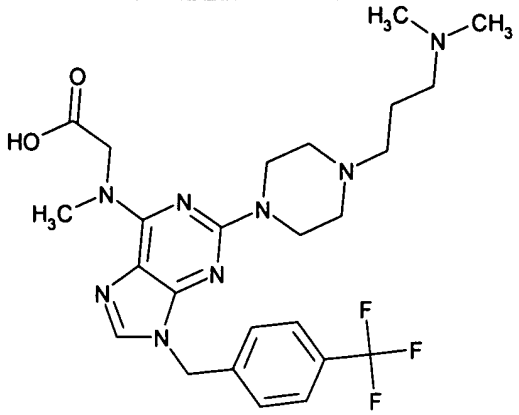
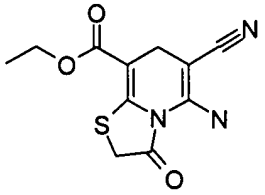
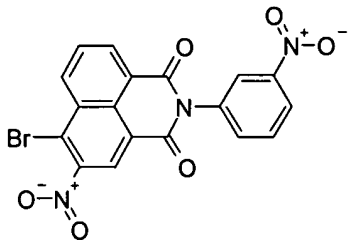
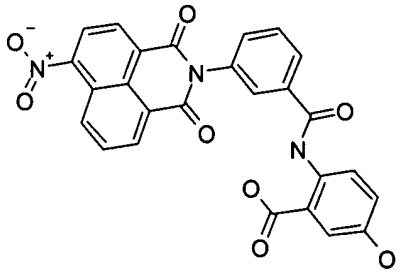
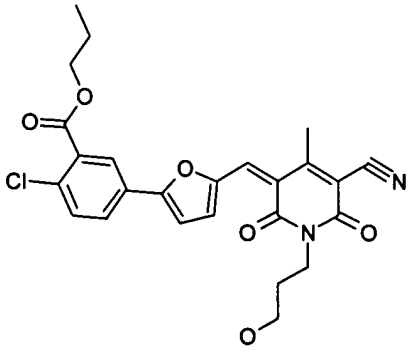
A9.035		14.6
A9.036		15.2
A9.037		16.0
A9.038		17.1
A9.039		17.9

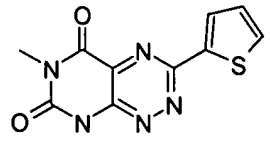
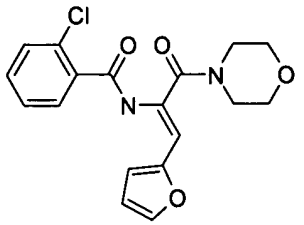
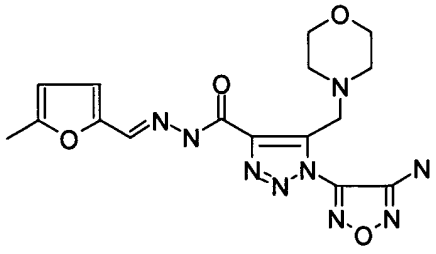
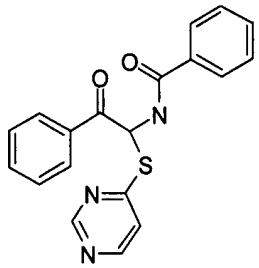
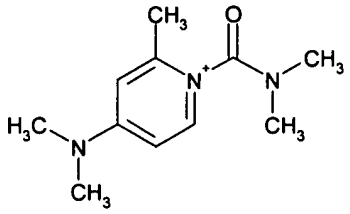
A9.040		18.1
A9.041		18.2
A9.042		18.2
A9.043		19.0
A9.044		19.1
A9.045		19.2

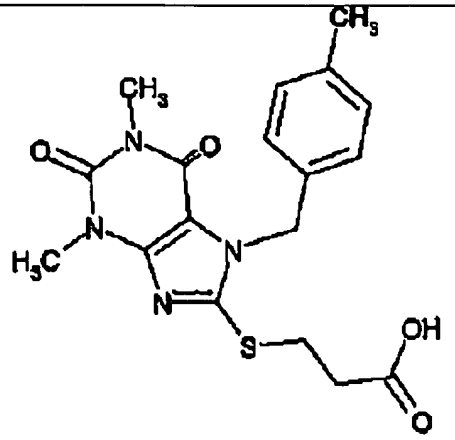
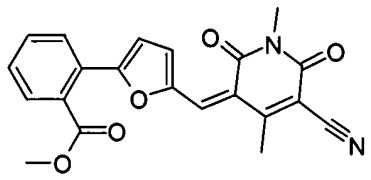
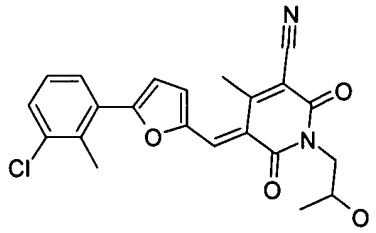
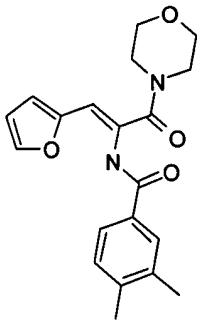
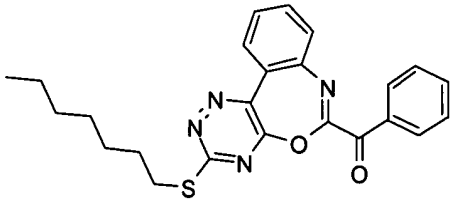
A9.046		19.2
A9.047		19.9
A9.048		20.3
A9.049		20.8
A9.050		20.9

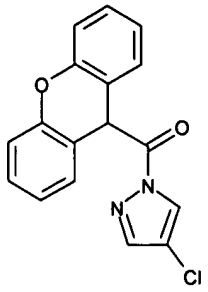
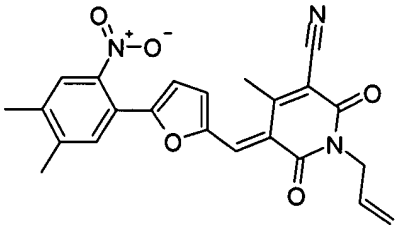
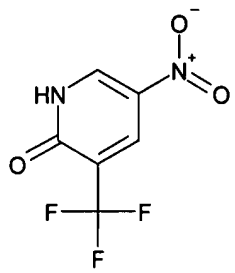
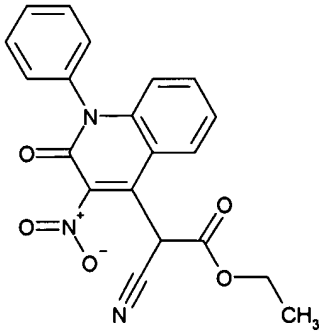
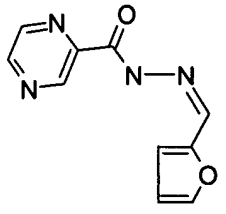
A9.051		21.1
A9.052		21.2
A9.053		21.3
A9.054		21.4

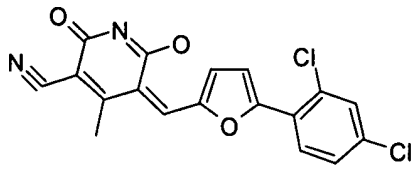
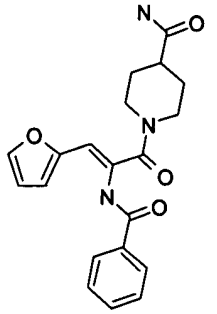
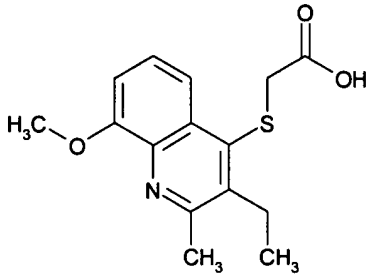
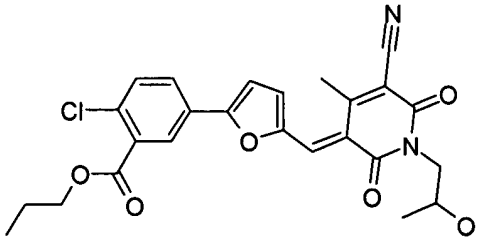
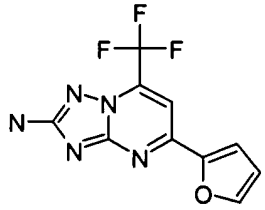
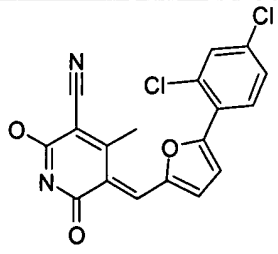
A9.055		21.6
A9.056		21.9
A9.057		22.3
A9.058		22.4
A9.059		25.0

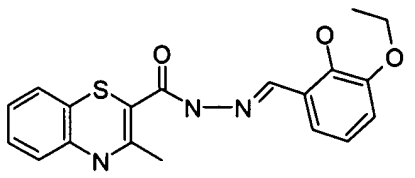
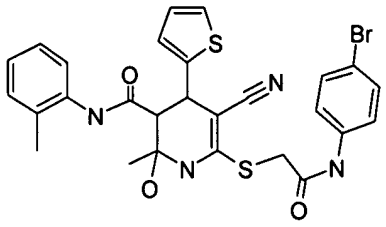
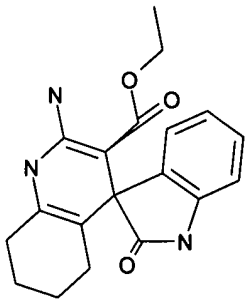
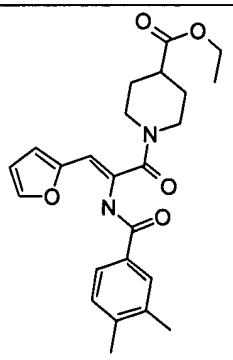
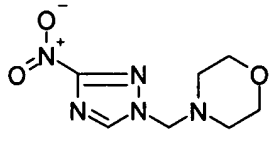
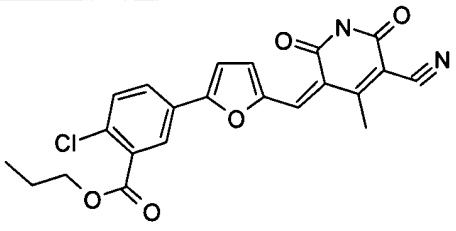
A9.060		23.0
A9.061		23.1
A9.062		23.3
A9.063		23.6
A9.064		23.8

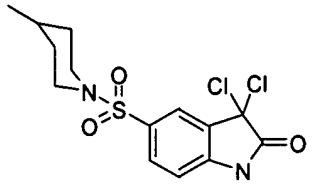
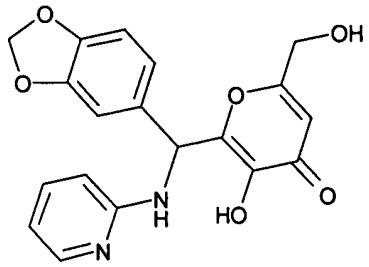
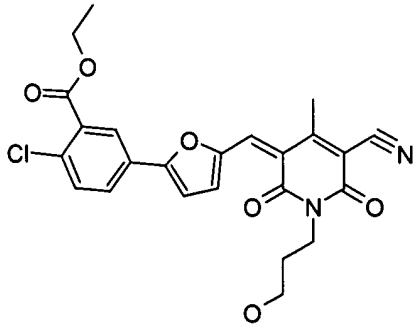
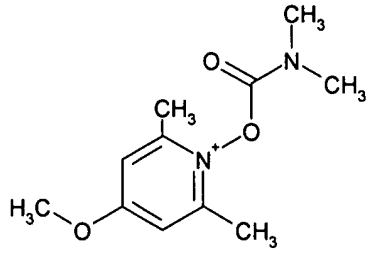
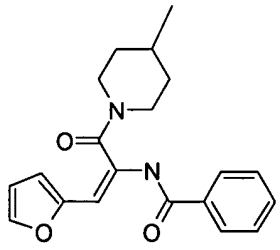
A9.065		22.6
A9.066		25.5
A9.067		26.7
A9.068		26.9
A9.069		27.6

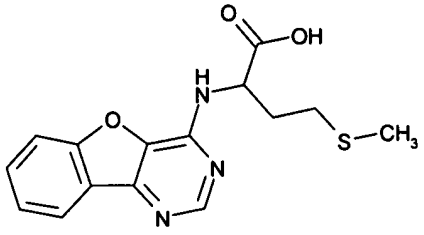
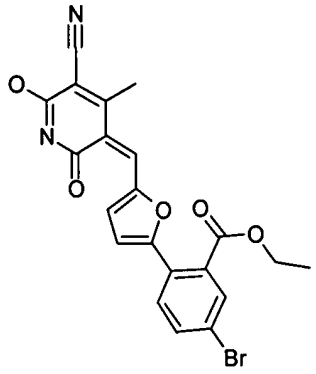
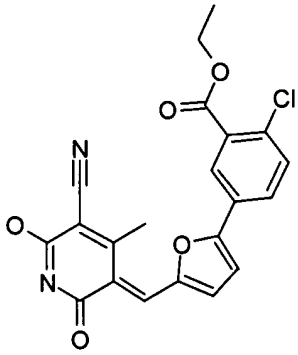
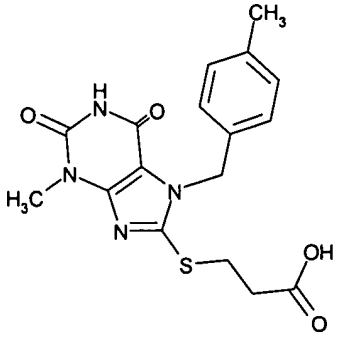
A9.070		28.0
A9.071		28.1
A9.072		28.6
A9.073		28.8
A9.074		28.9

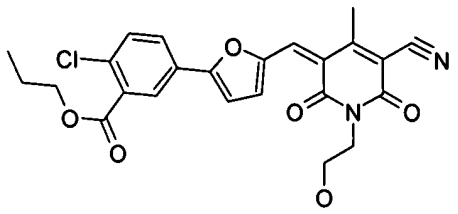
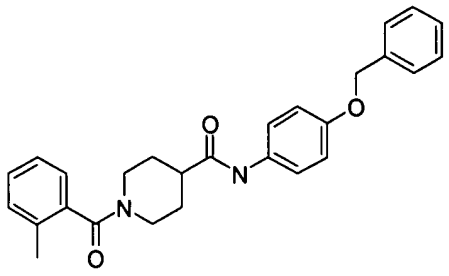
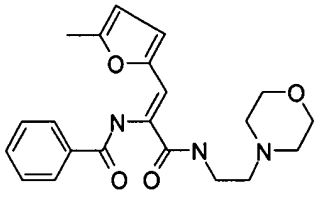
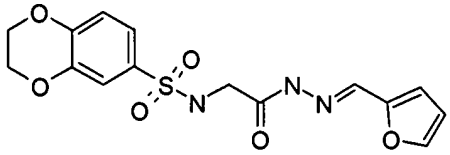
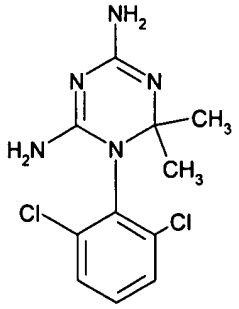
A9.075		29.1
A9.076		29.3
A9.077		29.9
A9.078		30.0
A9.079		30.1

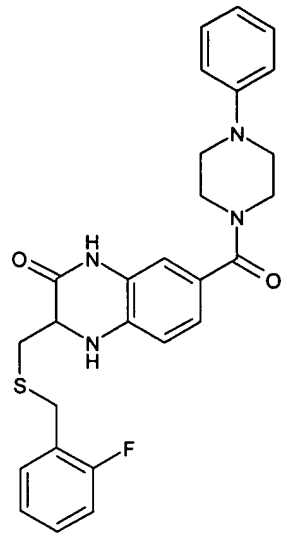
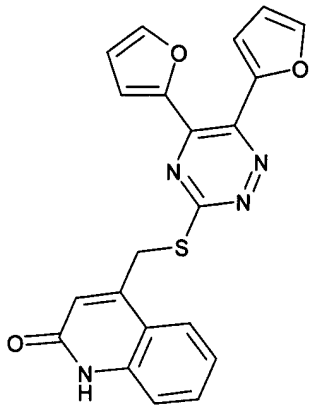
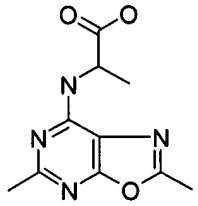
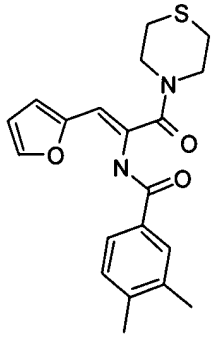
A9.080		30.3
A9.081		30.5
A9.082		31.1
A9.083		32.0
A9.084		32.1
A9.085		32.4

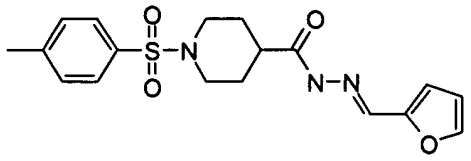
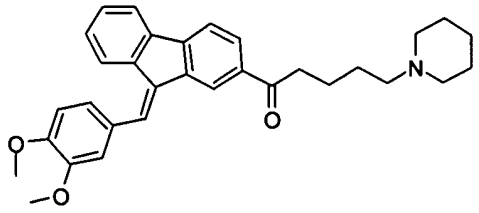
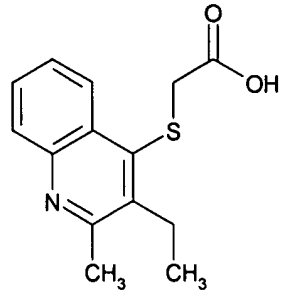
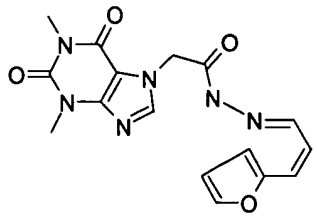
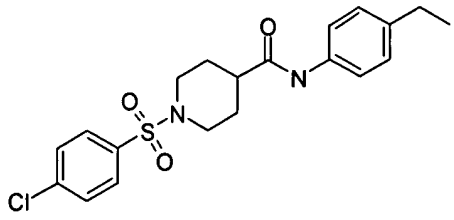
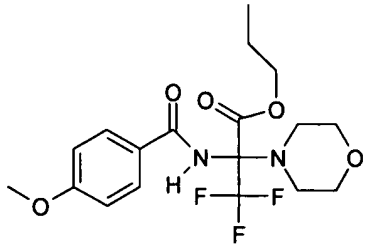
A9.086		33.2
A9.087		33.9
A9.088		33.6
A9.089		34.5
A9.090		36.8
A9.091		36.8

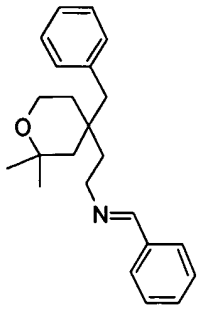
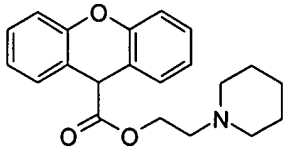
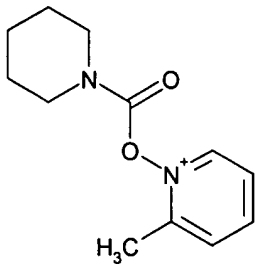
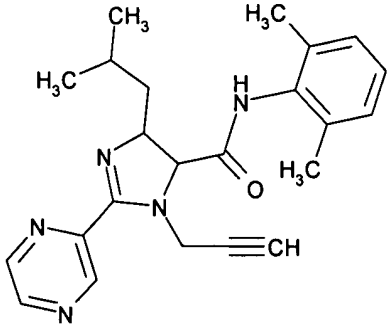
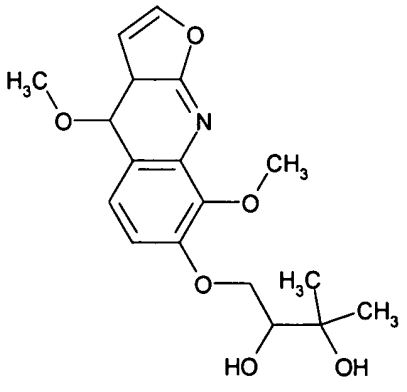
A9.092		37.2
A9.093		37.3
A9.094		41.0
A9.095		42.4
A9.096		45.0

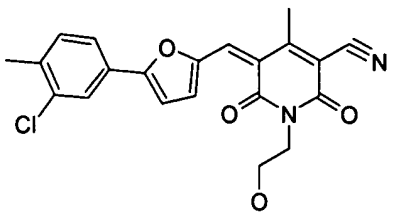
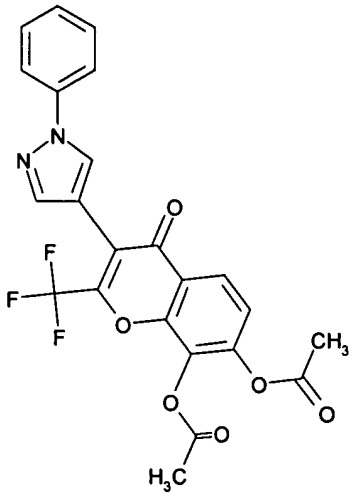
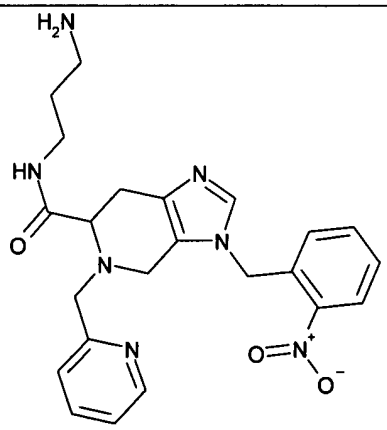
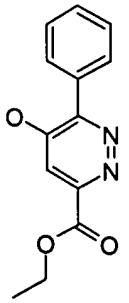
A9.097		48.4
A9.098		49.9
A9.099		52.1
A9.100		53.2*

A9.101		54.0
A9.102		54.0
A9.103		55.0*
A9.104		55.6
A9.105		59.8

A9.106		61.5
A9.107		65.1*
A9.108		65.8
A9.109		68.9

A9.110		69.3
A9.111		74.6
A9.112		77.4
A9.113		79.8*
A9.114		80.4*
A9.115		90.2

A9.116		93.6
A9.117		94.8*
A9.118		96.7*
A9.119		102.6*
A9.120		117.3*

A9.121		125.4
A9.122		133.7*
A9.123		138.4
A9.124		142.9

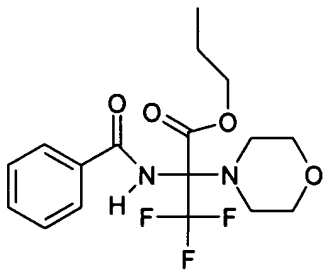
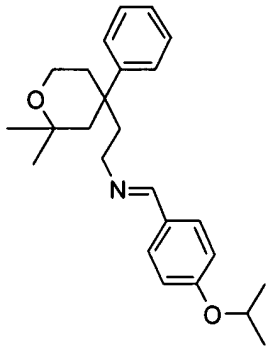
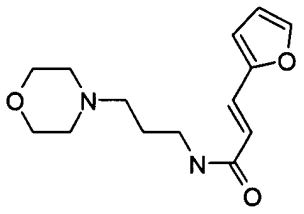
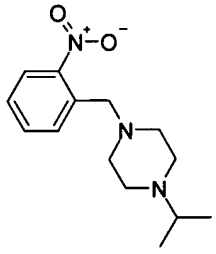
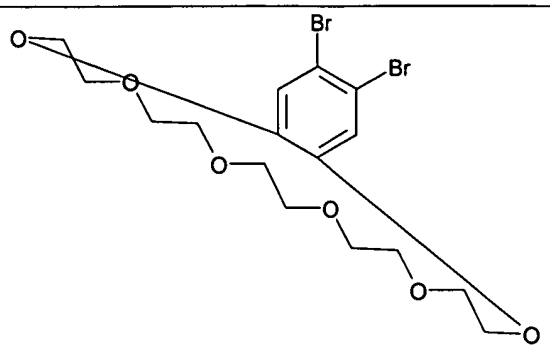
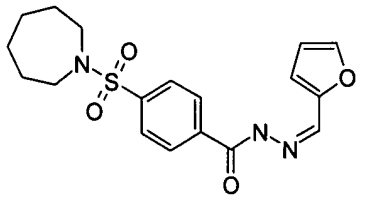
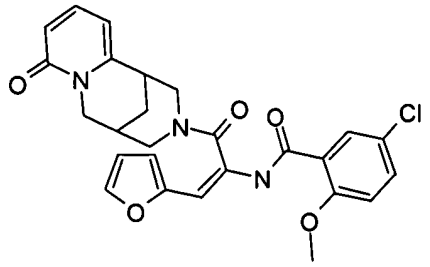
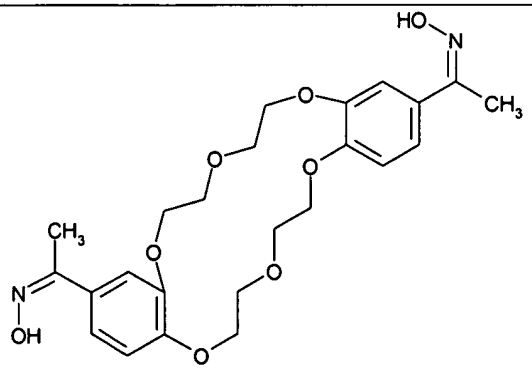
A9.125		186.0*
A9.126		197.4*
A9.127		208.5*
A9.128		252.2*

Table 10:

Compound ID.	Structure	$IC50_{APN}$ [µM]
A10.001		0.7
A10.002		8.0
A10.003		8.1
A10.004		8.6

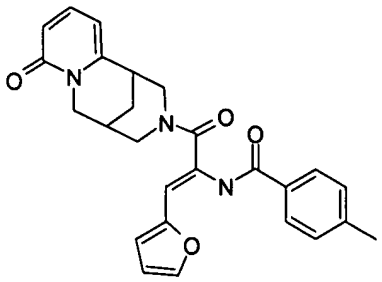
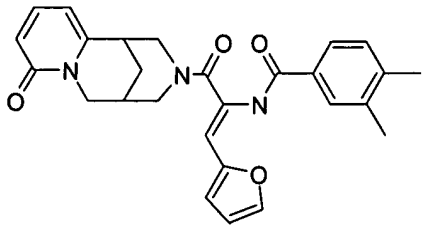
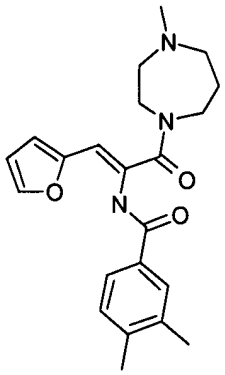
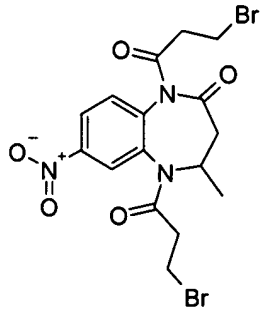
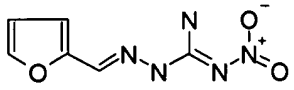
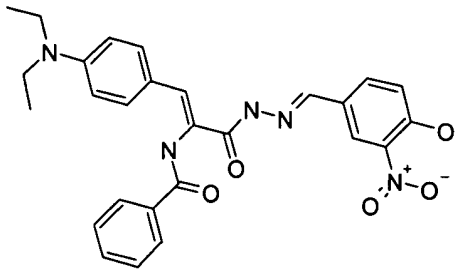
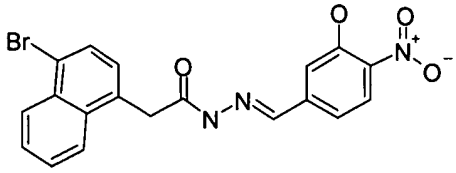
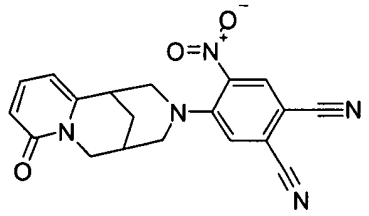
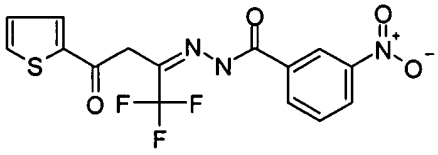
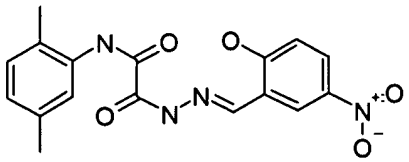
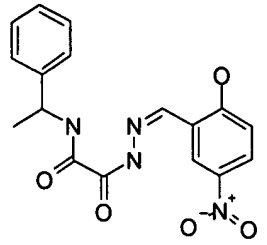
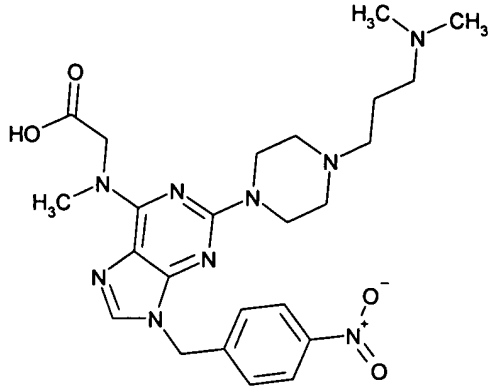
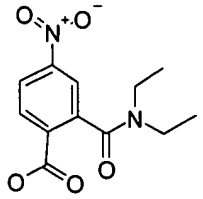
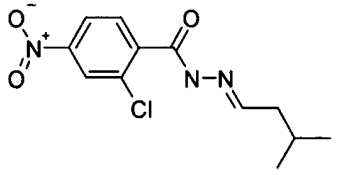
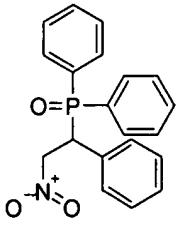
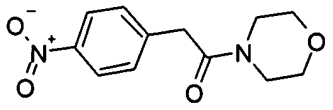
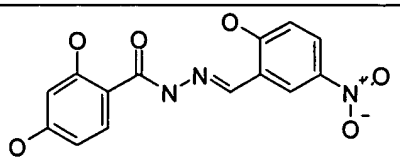
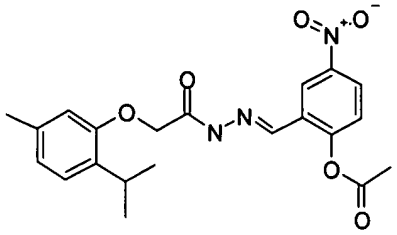
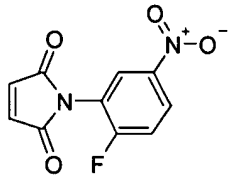
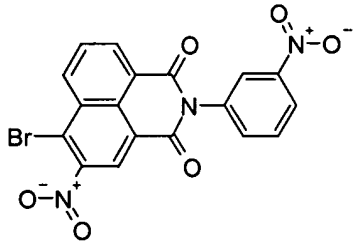
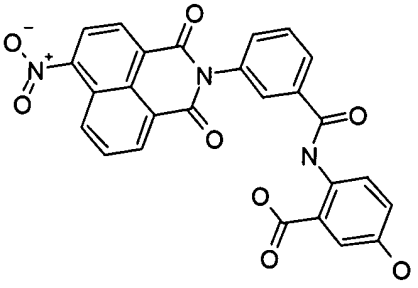
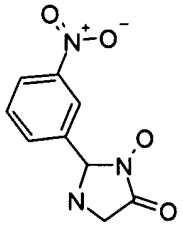
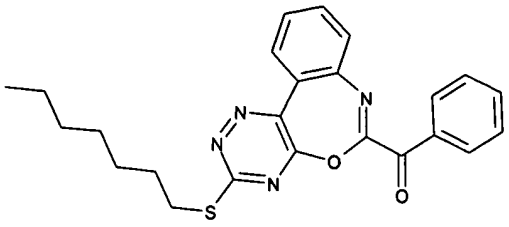
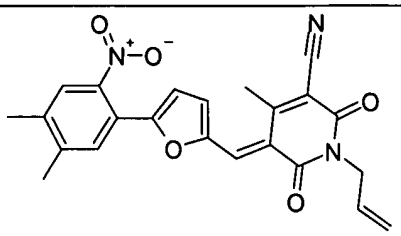
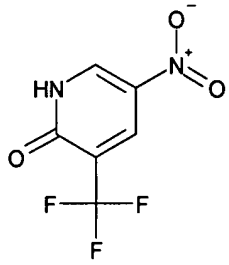
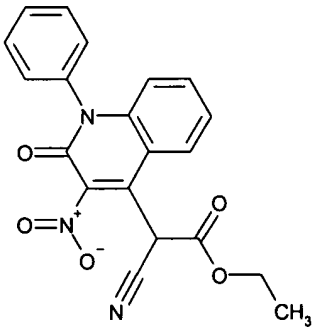
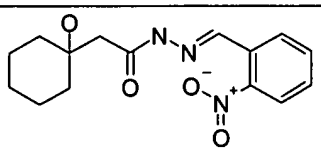
A10.005		11.0
A10.006		11.8
A10.007		32.1
A10.008		99.8*

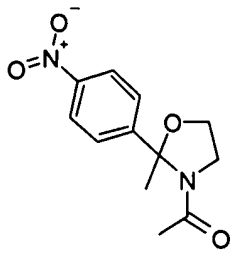
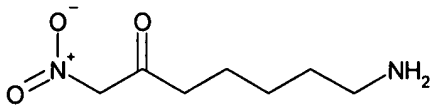
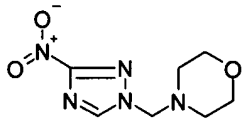
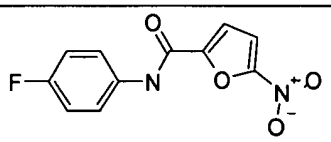
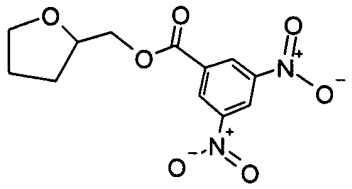
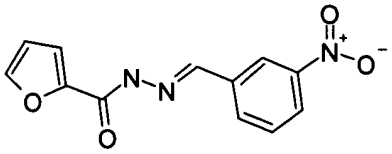
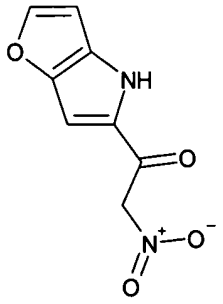
Table 11:

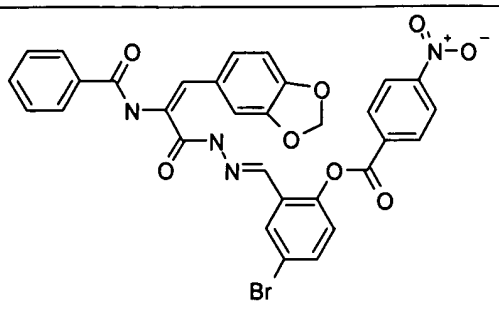
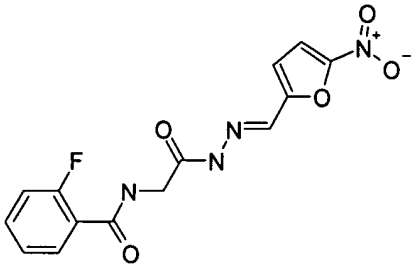
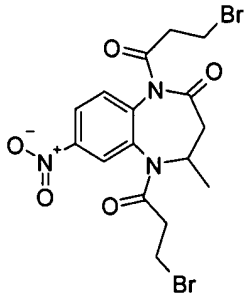
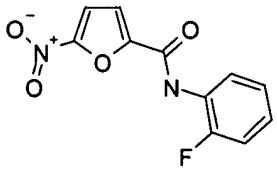
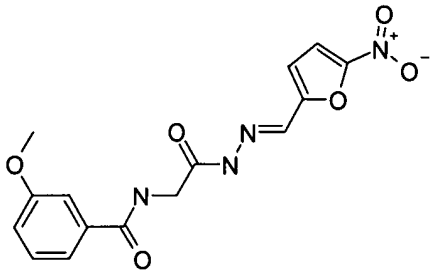
Compound ID.	Structure	$IC50_{APN}$ [µM]
A11.001		7.6
A11.002		7.6
A11.003		7.0
A11.004		8.9
A11.005		10.7
A11.006		10.8

A11.007		11.4
A11.008		11.8
A11.009		12.1
A11.010		15.6
A11.011		16.3
A11.012		19.1

A11.013		20.2
A11.014		20.3
A11.015		20.8
A11.016		23.3
A11.017		23.6
A11.018		26.4

A11.019		28.9
A11.020		29.3
A11.021		29.9
A11.022		30.0
A11.023		31.1

A11.024		32.8
A11.025		33.2
A11.026		36.8
A11.027		37.4
A11.028		39.3
A11.029		45.4
A11.030		49.5

A11.031		54.2
A11.032		60.0
A11.033		99.8*
A11.034		62.4
A11.035		221.8*

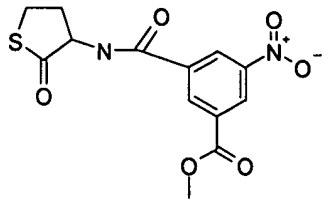
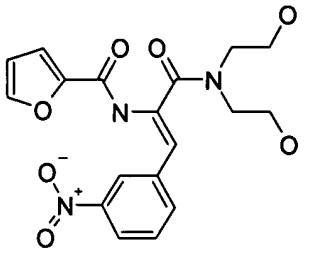
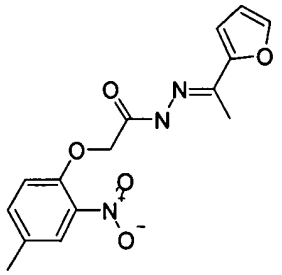
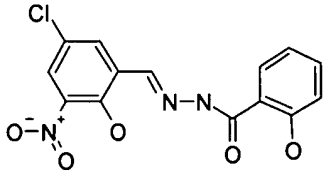
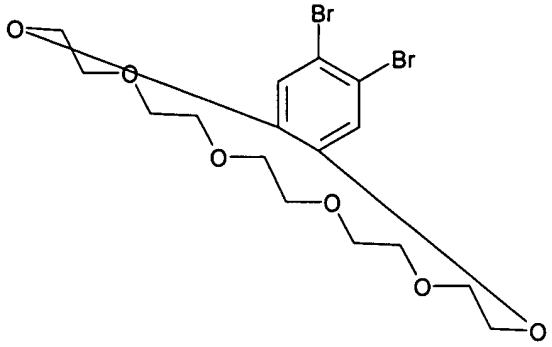
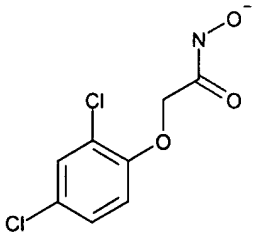
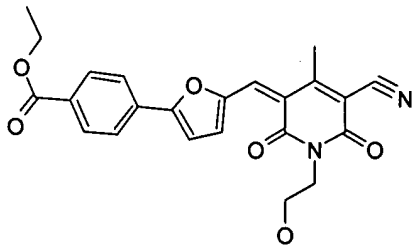
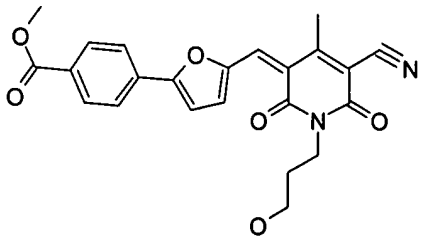
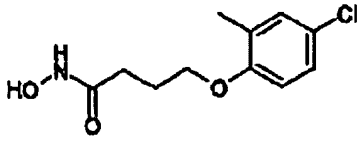
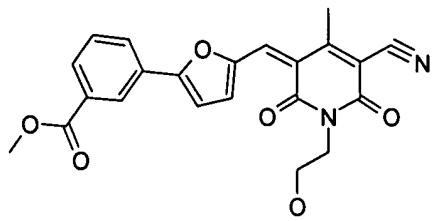
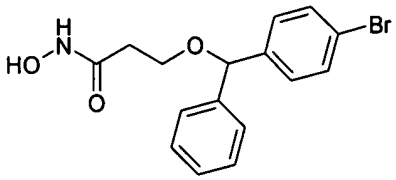
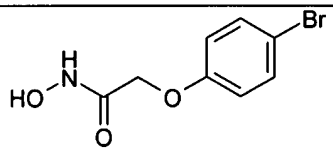
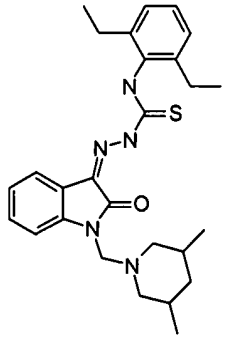
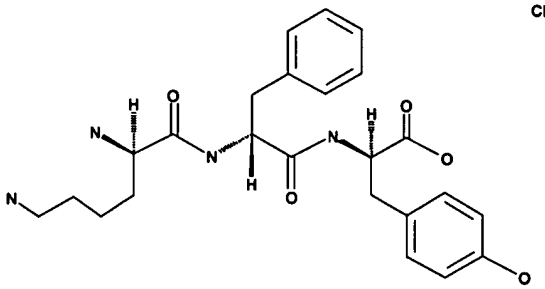
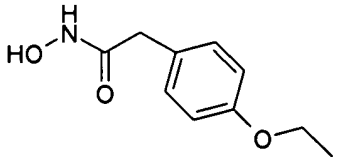
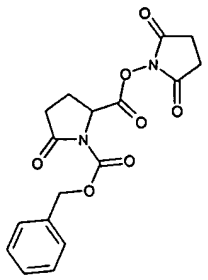
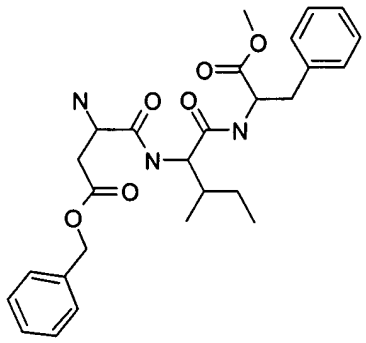
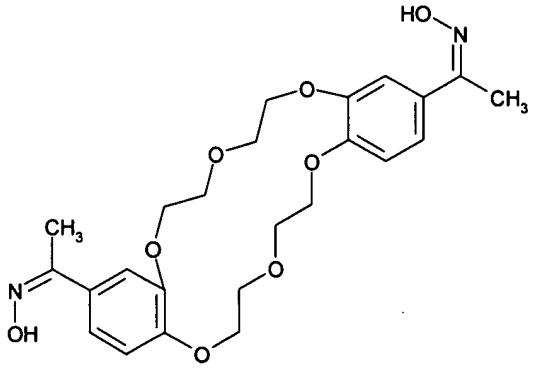
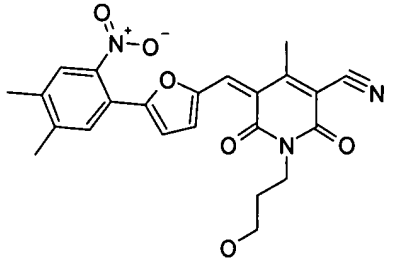
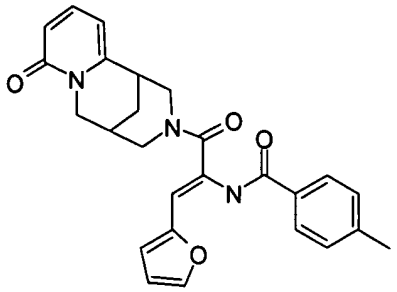
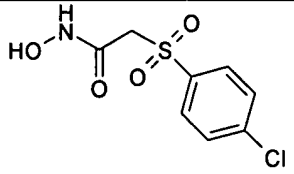
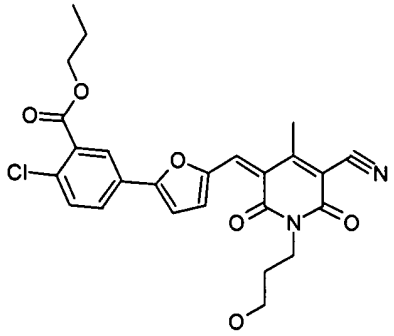
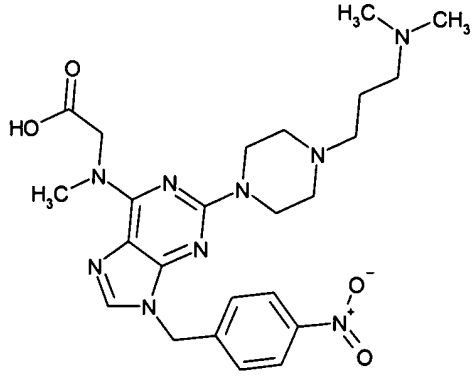
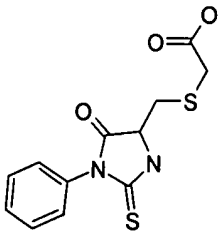
A11.036		238.4*
A11.037		243.8*
A11.038		422.4*
A11.039		5.8

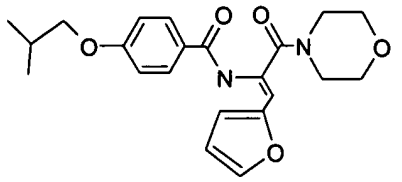
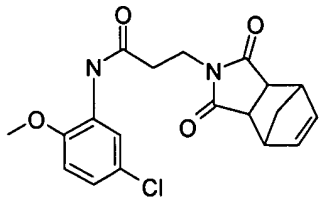
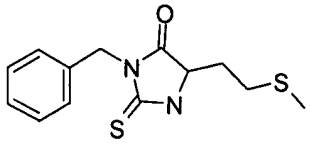
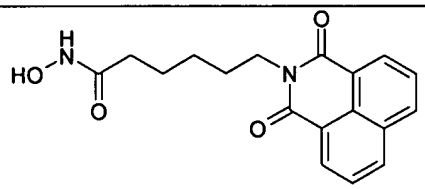
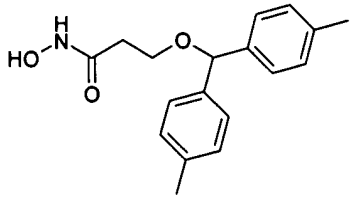
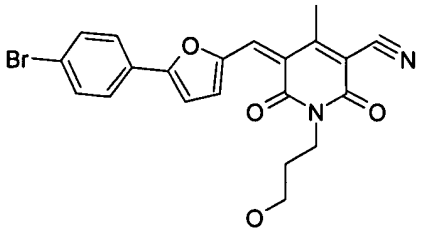
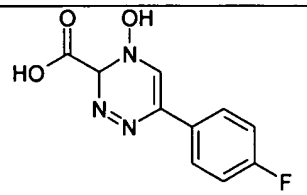
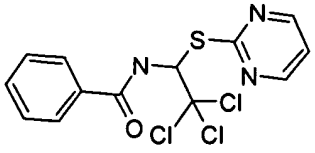
Table 12:

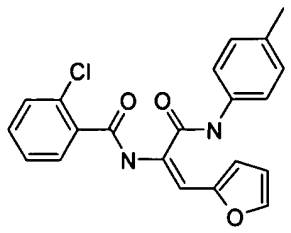
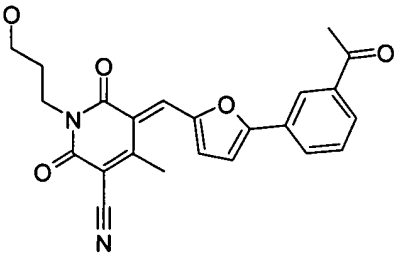
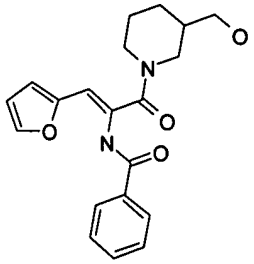
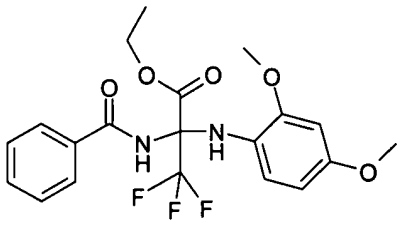
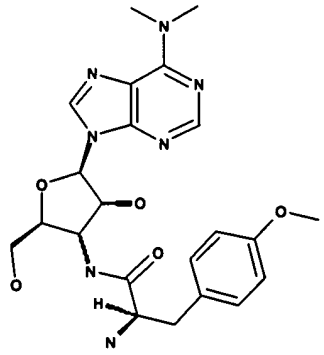
Compound ID.	Structure	$IC50_{APN}$ [µM]
A12.002		0.7*
A12.003		0.8*
A12.004		2.7*
A12.005		5.0
A12.006		5.6

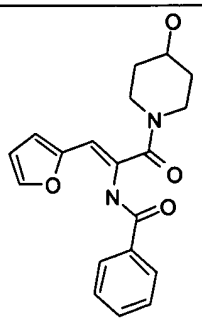
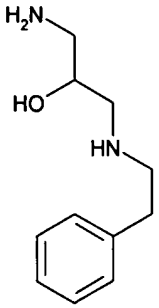
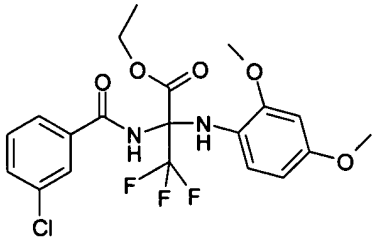
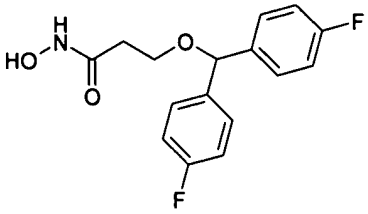
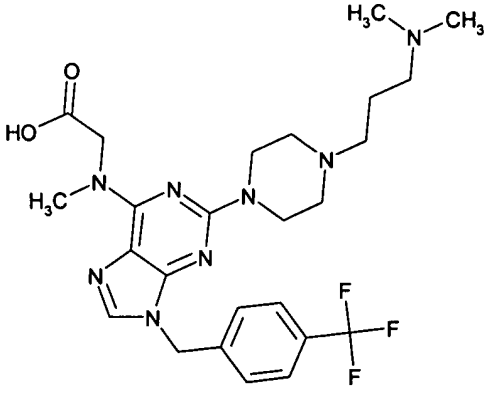
A12.007		6.3
A12.008		6.3
A12.009		6.4
A12.010		6.7
A12.011	Chiral 	7.3
A12.013		7.5

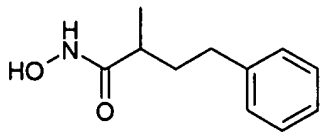
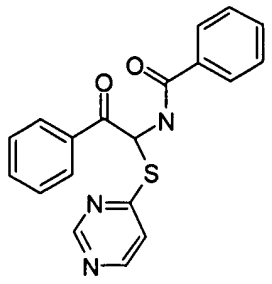
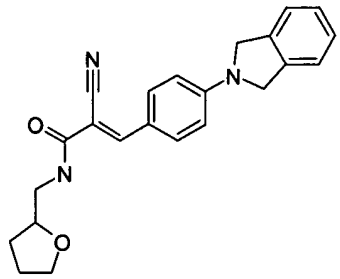
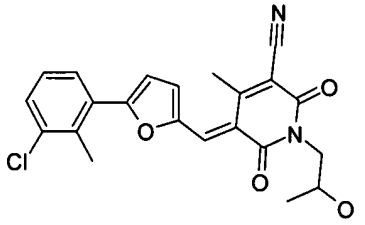
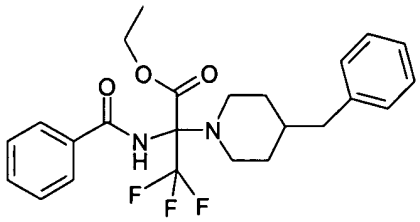
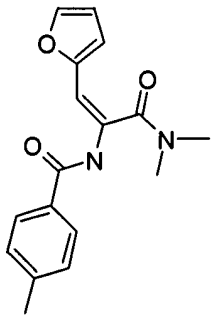
A12.015		7.5
A12.016		8.6
A12.017		8.6
A12.018		9.7

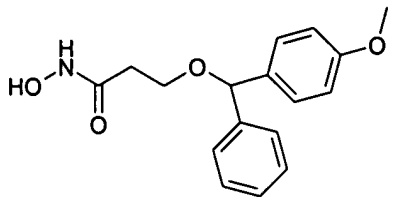
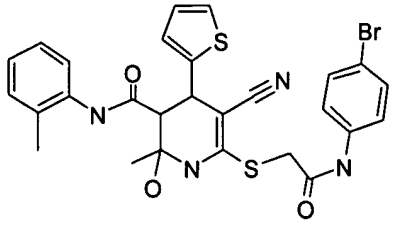
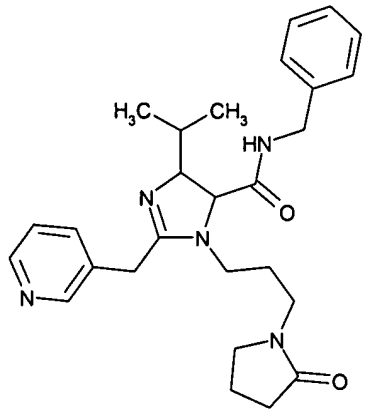
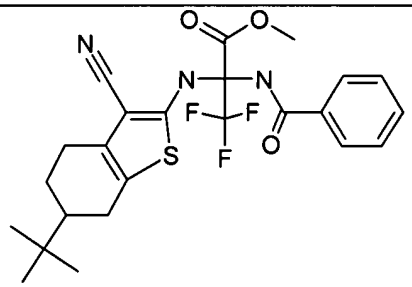
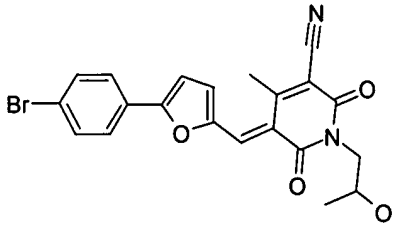
A12.019		11.0
A12.021		11.5
A12.022		23.8
A12.023		11.8
A12.024		12.0

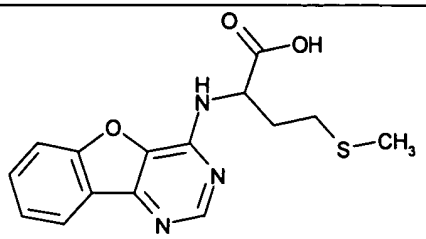
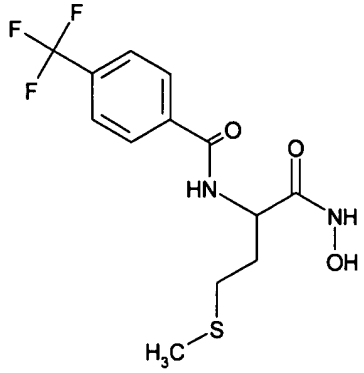
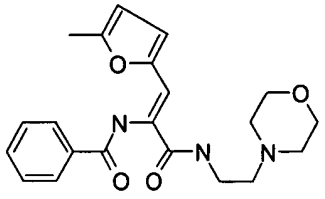
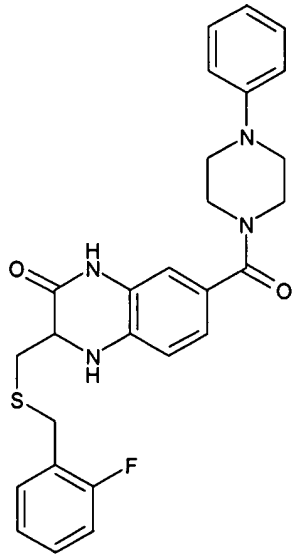
A12.025		13.1
A12.026		13.4
A12.027		14.1
A12.028		14.1
A12.029		14.2
A12.030		16.0
A12.031		17.1
A12.032		17.9

A12.033		17.9
A12.034		18.2
A12.035		19.0
A12.036		19.0
A12.037		20.9

A12.038		21.1
A12.039		21.2
A12.040		21.7
A12.041		21.8
A12.042		23.0

A12.044		25.2
A12.045		26.9
A12.047		28.1
A12.048		28.6
A12.049		29.9
A12.052		32.5

A12.053		33.0
A12.054		33.9
A12.055		34.0
A12.056		43.6
A12.058		47.2*

A12.060		48.4
A12.061		51.2
A12.063		55.0
A12.065		61.5

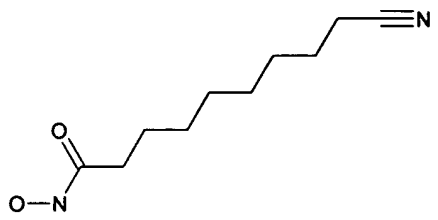
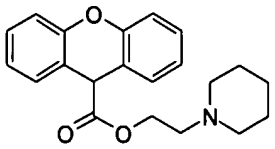
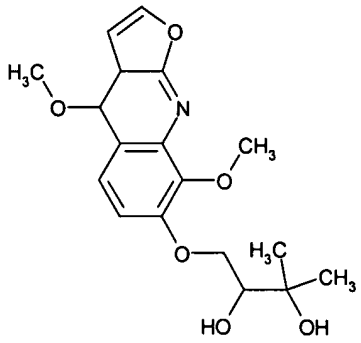
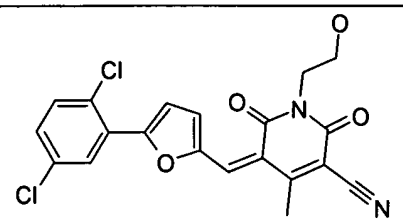
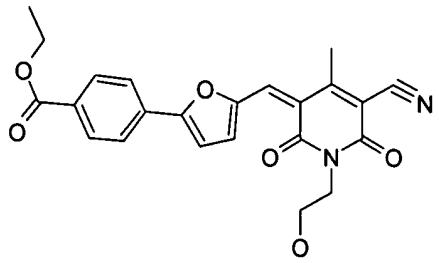
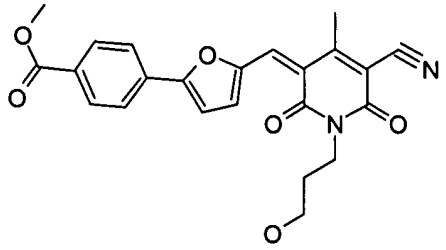
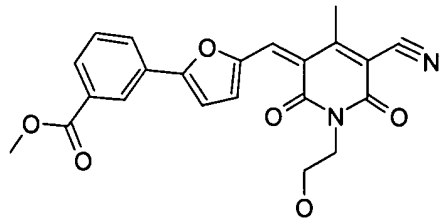
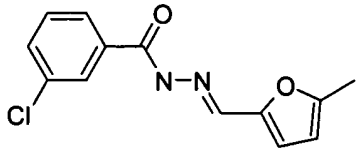
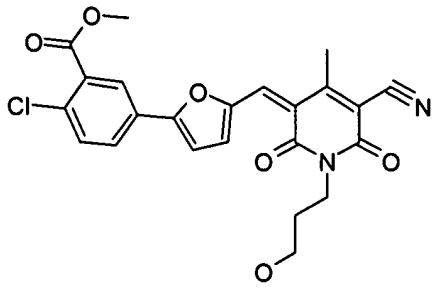
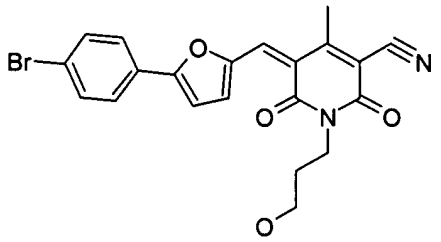
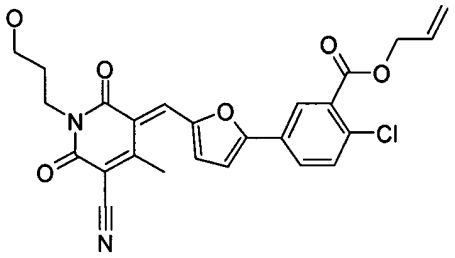
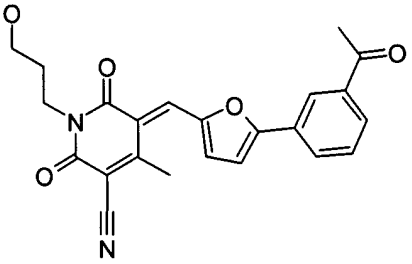
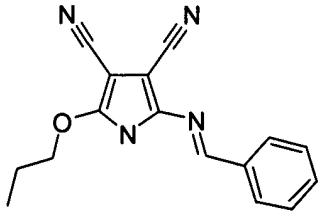
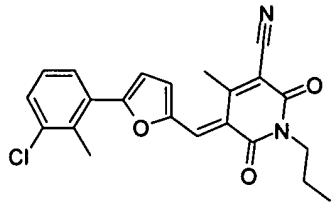
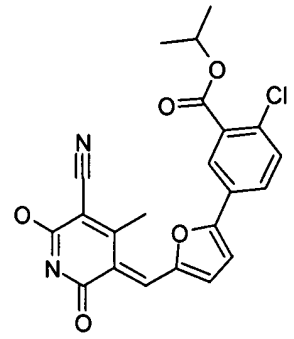
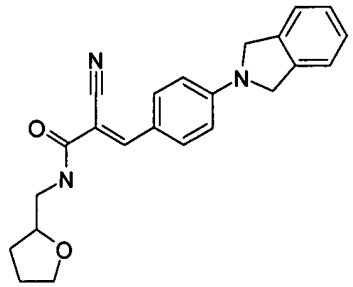
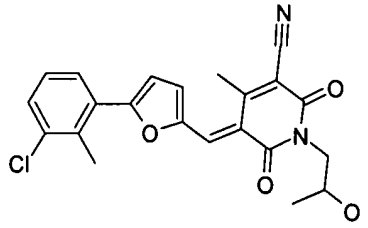
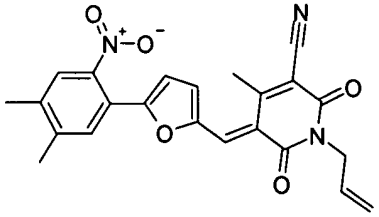
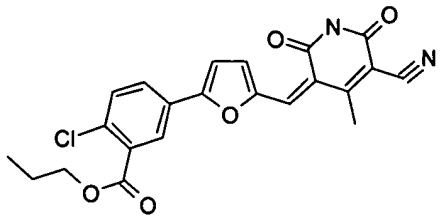
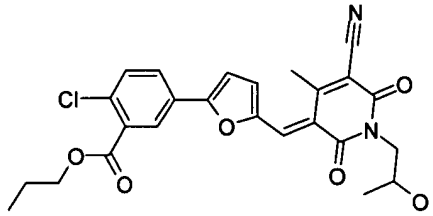
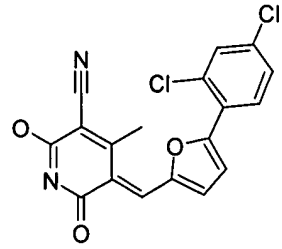
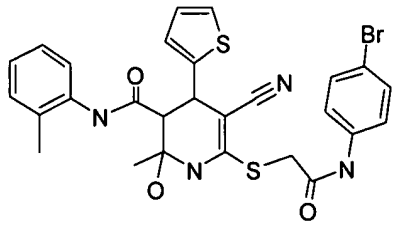
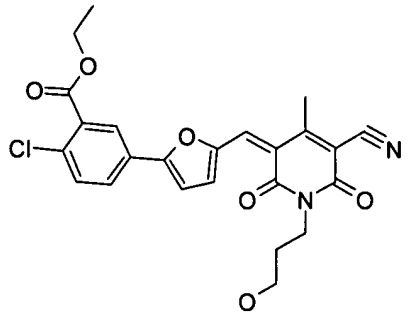
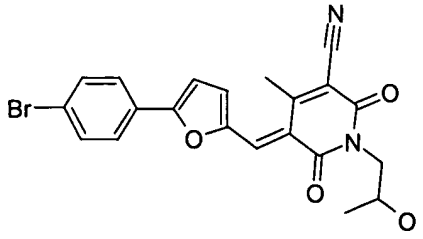
A12.069		80.6
A12.070		94.8
A12.072		117.3*

Table 13:

Compound ID.	Structure	$IC50_{APN}$ [µM]
A13.001		1.2*
A13.002		2.7*
A13.003		5.0
A13.004		6.3
A13.005		10.5

A13.006		15.2
A13.007		16.0
A13.008		18.1
A13.009		18.2
A13.010		20.0

A13.011		20.8
A13.012		21.4
A13.013		28.1
A13.014		28.6
A13.015		29.3

A13.016		36.8
A13.017		32.0
A13.018		32.4
A13.019		33.9
A13.020		41.0
A13.021		47.2*

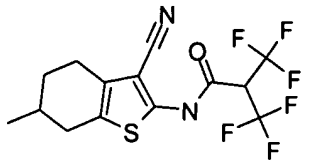
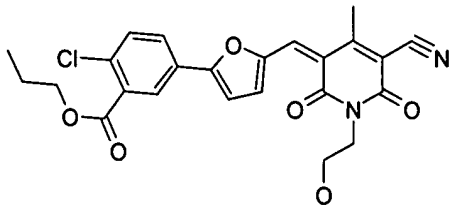
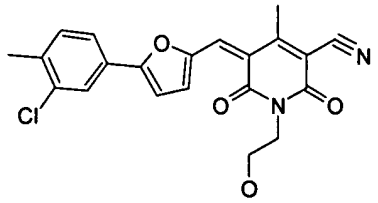
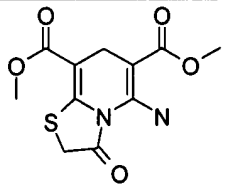
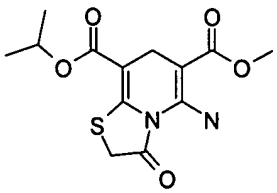
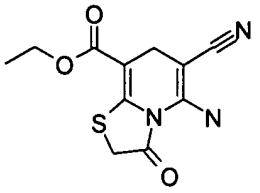
A13.022		51.3
A13.023		54.0
A13.024		125.4

Table 14:

Compound ID.	Structure	$IC50_{APN}$ [µM]
A14.001		"positively very highly active", means beyond measurement-scale"
A14.002		5.9

A14.003		23.1

Example 2:

Therapeutic effect of the combined inhibition of the alanyl aminopeptidases and of enzymes having an analogous effect as well as of the dipeptidyl peptidase IV and of enzymes having an analogous effect on the experimental autoimmune encephalomyelitis (EAE) of mice (animal model of multiple sclerosis)

The disease EAE was induced by a daily injection of PLP139-151 (myelin antigen proteolipide protein peptide 139-151) to SJL/J mice (n = 10). After the outbreak of the disease, there was, on the 11th day after the immunization, a therapeutic intervention by an intraperitoneal injection of 1 mg of each of the peptidase inhibitors on the first day and further injections of 0.5 mg of each of the inhibitors every second day. The disease scores [vD1] are defined by differently distinct degrees of paralysis. Healthy animals have the disease score 0. Actinonine was used as the alanyl aminopeptidase inhibitor, Lys[Z(NO_2)] pyrrolidide was used as the dipeptidyl peptidase IV inhibitor. The treatment was effected for the time of 46 days after the immunization. The results are shown in Figure 1. The course of the curves demonstrate unequivocally a most strong and long-lasting [vD2] therapeutic effect after a combined inhibition of both peptidases.

Example 3:

Therapeutic effect of the combined inhibition of the alanyl aminopeptidases and of enzymes having an analogous effect as well as of dipeptidyl peptidase IV and of enzymes having an analogous effect on the dextran sulfate-induced colitis in mice (animal model of chronic inflammatory intestinal diseases)

An inflammation relating predominantly to the colon (equivalent to the disease of human Colitis ulcerosa) was induced by an administration of 3 % sodium dextran sulfate dissolved in the drinking water of female Balb/c mice having an age of 8 weeks. After three days, all animals showed clear symptoms typical for the disease. The peptidase inhibitors (or phosphate-buffered saline as a placebo) were administered intraperitoneally from day 5 on for three successive days. The degree of the disease was determined in accordance with an acknowledged evaluation system (score). The following parameters were considered when determining the score: Consistency of the excrements (solid = 0 points (pts.); pasty = 2 pts.; liquid/like diarrhea = 4 pts.); detection of blood in the excrements (no blood = 0 pts.; occult blood = 2 pts.; evident = 4 pts.); loss of weight (0 – 5 % = 0 pts.; 5 to 10 % = 1 pts.; 10 – 15 % = 2 pts.; 15 – 20 % = 3 pts.; > 20 % = 4 pts.). Healthy animals have a score value of 0 pts.; the maximum value are 12 pts.. From 10 pts. on, the disease is lethal. In the course of the disease, the score value increased due to the change of the excrement parameters. Later-on (starting from day 5), the loss of weight increased the score. Figure 2 shows the disease intensity for untreated and treated animals on the day 7 after three days of therapy.

The application of 10 µg of the respective single prior art inhibitors (n = 14 per group; see explanation) achieved a slight, but insignificant reduction of the heaviness of the disease (- 16.5 % by a treatment with actinonine; - 12.3 % by a treatment with Lys[Z(NO_2)] pyrrolidide). An i.p. application of a combination of the two peptidase inhibitors resulted into a statistically significant (p = 0.00189) improvement of the disease by 40 %.

Example 4:

Therapeutic effect of the combined inhibition of alanyl aminopeptidases and of enzymes having an analogous effect as well as of dipeptidyl peptidase IV and of enzymes having an analogous effect on the ovalbumine-induced asthma bronchiale ib mice (animal model of human asthma bronchiale). Figure 3 shows the influence of the combined peptidase inhibition on the reduction of the average expiratory flux (EF 50) as a measure of the pulmonal function (Figure 3 A) as well as on the eosinophilia as a characteristic feature of the asthma bronchiale pulmonal inflammation (Figure 3 B).

Female Balb/c mice were sensitized for the antigen ovalbumine capable of inducing asthma bronchiale by an intreperitoneal administration of 10 µg ovalbumine on the days 0, 14 and 21. On day 27/28, the animals received a boostering dose of ovalbumine by inhalation [vD3]. After an intreperitoneal administration of the peptidase inhibitors on the days 28 – 35, there was effected an intranasal ovalbumine challenge on day 35, as well as a check of the allergic premature reaction via the pulmonal function. There were measured: the average expiratory flux (EF50), the tidal volume, the respiration rate and the minute volume as well as the number of eosinophilic granulocytes in the bronchoalveolar lavage.

8 to 10 animals were used per experimental group. By way of example, in Figure 3 A, there is summarized the effect of the peptidase inhibitors on the reduction of the EF50 value. The alanyl aminopeptidase inhibitor actinonine (group B; 0.1 mg), and the dipeptidyl peptidase IV inhibitor Lys[Z(NO_2)] pyrrolidide as well (group C; 0.1 mg), showed a therapeutic effect. Significant therapeutic effects, however, were obtained only when using combinations of both inhibitors (group D; 0.1 mg of each of the inhibitors). Group E represents animals which were not sensitized by OVA, but which were subjected – beyond that – all procedures to which the animal groups A to D were subjected. Hence, this group is a group of healthy, non-allergic animals allowing to calculate stress-induced effects on the pulmonal function.